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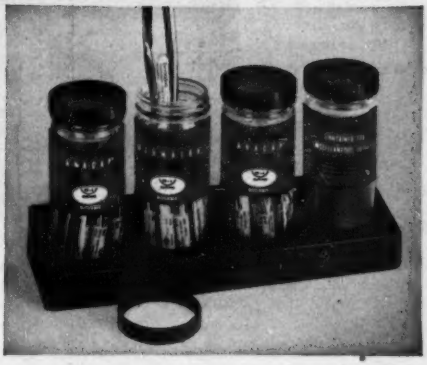

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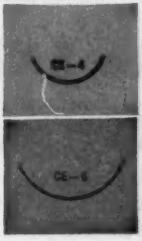

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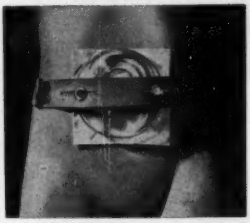

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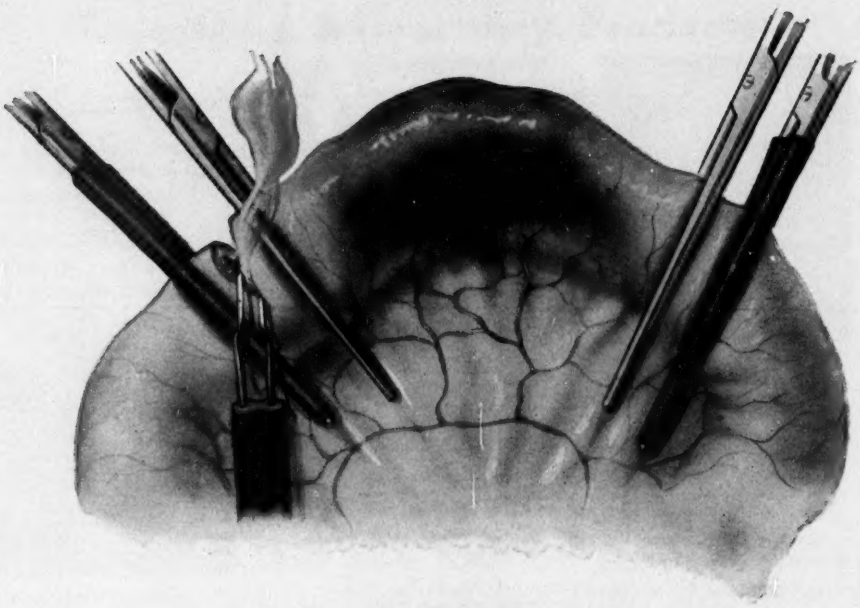

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EFFECT OF CORTISONE AND CORTICOTROPHIN (ACTH) ON INTRA-ABDOMINAL ADHESIONS

SCHAYEL R. SCHEINBERG, M.D.
AND
HARRY C. SALTZSTEIN, M.D.
DETROIT

AFTER a series of Mann-Williamson dogs were treated with cortisone, it was noticed that when the animals were killed several weeks later there was a marked reduction in the number and extent of intra-abdominal adhesions compared to those in the controls or in animals treated with any other therapy or type of medication. Accordingly, the role of cortisone and corticotrophin (ACTH) in the prevention of experimental intra-abdominal adhesions was investigated.

PROCEDURE

Adhesions were produced in 30 mongrel dogs, 20 to 22 lb. (9 to 10 kg.) in weight, by sprinkling 0.25 gm. of talcum U. S. P. evenly over one side of the serosal surface of the small bowel and its mesentery from the ligament of Treitz to the cecum (method of Schiff, Goldberg and Necheles.[1]). Ten dogs were used as controls, 10 received 10 mg. of cortisone intramuscularly twice daily for two weeks, and 10 received 5 mg. of corticotrophin twice daily. The dose of cortisone and corticotrophin was determined as follows: Six dogs were given 10 mg. of cortisone and an eosinophile count was done four hours later. There was a 50% drop or more in each instance. Six dogs given 5 mg. of cortisone each showed no drop in eosinophils. Four dogs were given 5 mg. of corticotrophin, and all showed a drop of 50% or more in the eosinophile count in four hours. Four were given 2.5 mg., and none showed a drop in eosinophils. Four dogs were given 5 mg. of corticotrophin, and all showed a drop of 50% or more in the eosinophile count in four hours. Four were given 2.5 mg., and none showed a drop in eosinophils. Therefore, the effective dose of cortisone was taken to be 10 mg. twice a day and of corticotrophin, 5 mg. twice a day.

Dr. Carlozzi of Merck & Company, Inc., generously supplied us with cortisone.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1951.

From the Experimental Surgical Laboratory, Harper Hospital, aided by the Max Unger Fund and by a Research Grant from the National Institutes, United States Public Health Service.

1. Schiff, C. A.; Goldberg, S. L., and Necheles, H.: The Prevention of Abdominal Adhesions, Surgery **25**:257, 1949.

The animals were killed from two to six weeks after operation, as follows:

Day Killed	Controls	Treated with Cortisone	Treated with Cortico-trophin
After 2 wk.	2	5	3
After 4 wk.	4	5	4
After 6 wk.	4	0	3

Fig. 1.—Control dog, killed 14 days after application of talcum powder. Note dense mass of adherent loops.

RESULTS

In all the control animals, when killed, the small bowel was one dense mass of adherent loops. The mesentery was glued together; it had lost its transparency and was thick and matted. The bowel loops could not be brought out onto the abdomen except en masse and to a limited extent. The undersurface of the liver was glued to the bowel and the bowel glued to the anterior peritoneum in all animals (Fig. 1).

All the cortisone-treated animals showed normal transparent thin serosa; the entire loop could be brought out of the abdomen easily. There was no agglutination between the bowel loops, the undersurface of the liver and the anterior abdominal

wall. Adhesions were present, but they were thin, filmy ones which could easily be separated by the fingers, and although the bowel loops were stuck together in some places, the density was much less (Fig. 2). The animals treated with corticotrophin showed the same results.

In order to get a numerical comparison, adhesions were counted as one if they were 1 cm. or less in length, as two if they were up to 2 cm., as three up to 3 cm., and as four up to 4 cm., regardless of width. They were graded 1 to 4 plus,

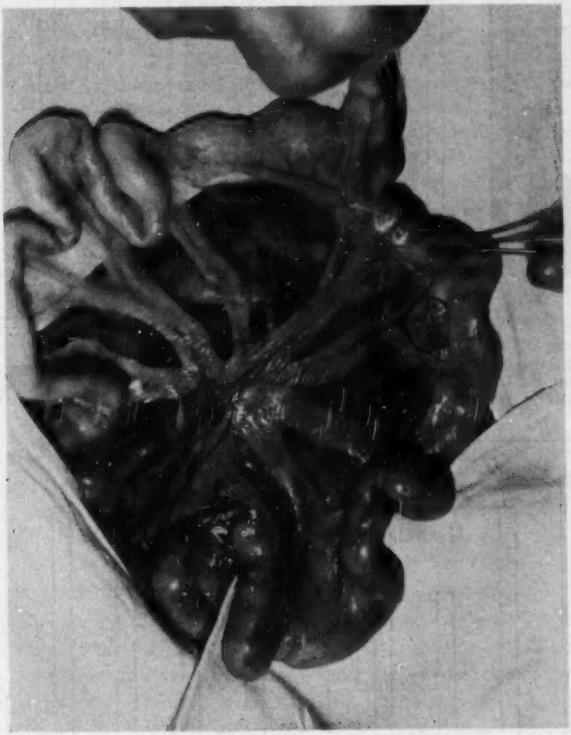

Fig. 2.—Dog killed on 14th day after administration of 10 mg. of cortisone twice daily. Note scarcity of adhesions, with the smooth, thin, glistening mesentery.

4 being the maximum. The number of sharp-angled or hairpin turns of small bowel loops also were tabulated.[1] Estimated in this way, the cortisone-treated dogs and the corticotrophin-treated dogs showed 75% less adhesions and 60% less hairpin turns than did the controls. The results of the experiments are summarized and tabulated in Figures 3 and 4. In the cortisone-treated dogs, the average number of adhesions and hairpin turns produced was 15.0 and 3.2, as compared to 45.3 and 8.3, respectively, in the controls. There was a uniformity of findings in both the cortisone and the corticotrophin-treated animals. They showed approximately the

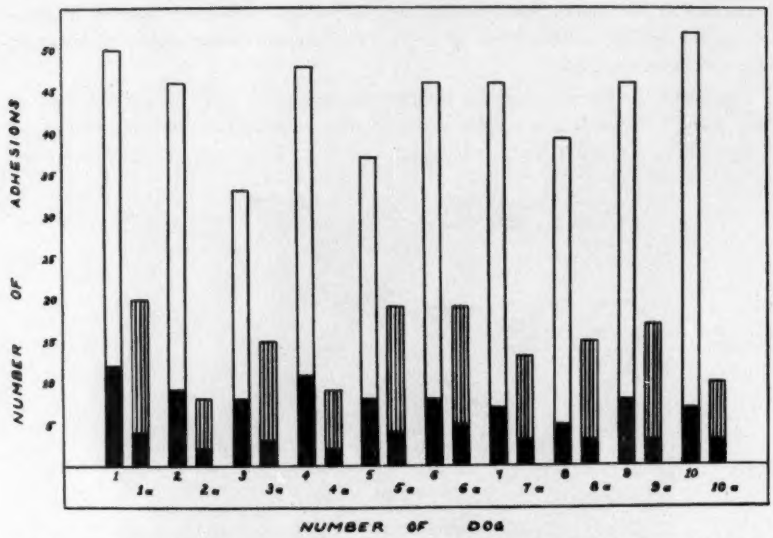

Fig. 3.—Each column represents one dog. White column indicates control dogs (*1* etc.) and striped column, dogs treated with cortisone (*1d* etc.). Solid portion denotes number of hairpin turns.

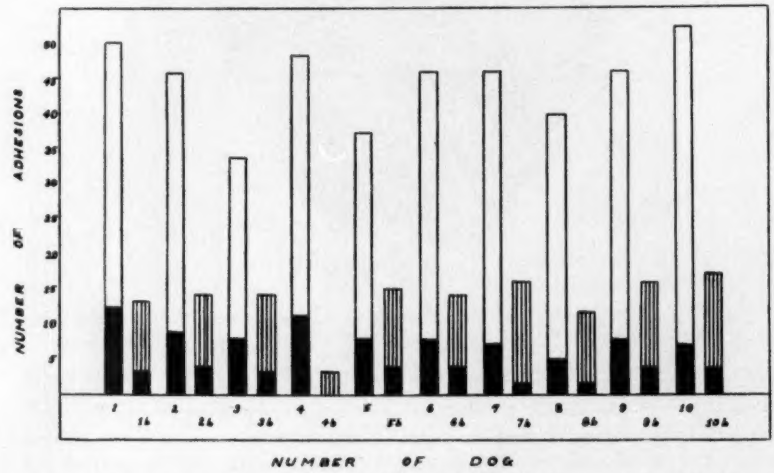

Fig. 4.—Each column represents one dog. White column indicates control dogs (*1* etc.) and striped column, dogs treated with corticotrophin (*1b* etc.). Solid portion denotes number of hairpin turns.

same number of adhesions and hairpin turns and the same ease of separation of their adhesions.

These questions then presented themselves: 1. What is the dosage necessary to prevent adhesions? 2. What is the duration of treatment necessary to prevent adhesions? 3. When do adhesions first appear? 4. Will wound healing be delayed by the dosage necessary to prevent adhesions? The following experiments are reported in a preliminary fashion; more work will be necessary to answer these questions definitely.

Experiments on Rats.—A series of 20 rats (pure bred white "Wistar" strain) were given an intraperitoneal injection of 0.5 cc. of 10% saline suspension of talcum powder. Ten received 2 mg. of cortisone daily for 13 days, and 10 were kept as controls. All were killed on the 13th day. In the control rats the same dense abundant adhesions were noted as in the control dogs. In these 10 animals there was a total of 55 adhesions and 26 hairpin turns, and seven had intestinal obstruction due to adhesions. In the 10 treated rats there was a total of two adhesions and no hairpin turns, and none had intestinal obstruction. Thus the same significant prevention of adhesions was noted in the cortisone-treated animals as we had observed in dogs.

1. Dosage: Six rats were given 0.5 mg. of cortisone daily intramuscularly for 13 days, six were given 1 mg. daily, and six were given 2 mg. daily. In the animals receiving 2 mg. daily there was a total of only two adhesions compared to five adhesions in the animals treated with 1 mg. and a total of 28 adhesions in those treated with 0.5 mg. These experiments show that although 1 mg. of cortisone daily partially protected against adhesions, 2 mg. daily was necessary for protection with a degree of assurance.

2. Duration of Treatment Necessary: Six rats received 2 mg. of cortisone for seven days and then were killed on the seventh day after the talcum injection (talc suspension), and six received the same dose for seven days and were killed on the 14th day. In the first group none of the animals showed adhesions. Of the group killed on the 14th day, three had adhesions. Evidently the stimulus to adhesion formation was not entirely prevented by seven days' treatment in these rats.

3. First Appearance of Adhesions: Six series of six rats each (36 rats) were given an injection of the talcum powder suspension intraperitoneally. Three in each series were kept as controls, and three were given 2 mg. of cortisone intramuscularly daily. Each series (three controls, three treated) were killed at 3, 4, 6, 8, 10 and 12-day intervals after talc injection. As early as the third day the controls showed agglutination of the small bowel loops to each other, causing hairpin turns. Definite adhesions first appeared on the sixth day. In the treated animals there were no signs of adhesions until the eigth day, and then they were minimal. After the 10th day, there were no adhesions apparent in the treated animals.

4. Delay in Wound Healing: Wounds were produced by making a skin defect on the abdominal wall of 28 rats. A 1.5 cm. steel cork borer was turned through the skin and the circular defect excised (method of Scheinberg, Bralow, and Necheles).[2] The animals were divided into groups of four each, as follows: Group

2. Scheinberg, S.; Bralow, S. P., and Necheles, H.: Experimental Study of Wound Healing, Surgery **24**:972, 1948.

A consisted of control animals, and groups B, C, D, E, F, and G were given 0.5, 1, 2, 3, 4, and 5 mg. of cortisone intramuscularly daily. All were examined on the 12th day. In groups A, B, C, and D, given up to 2 mg. of cortisone, there was complete healing, with epithelization of all wounds. Groups E, F and G, given 3 mg. and over daily, showed unhealed areas measuring up to 1 cm. in all animals. Therefore, in 150 gm. white rats injection of 2 mg. of cortisone intramuscularly daily will prevent intraperitoneal adhesion formation without delay in healing, whereas injection of 3 mg. and over daily for 12 days will delay healing.

COMMENT

Sprague and others [3] have shown that in man large doses (200 mg. of cortisone, 105 mg. of corticotrophin) "result in a rather decided loss of nitrogen from the body, indicative of an increase in the catabolism of protein." Pronounced creatinuria and an increase in the excretion of uric acid were also observed. They believe that this effect of the two hormones on protein metabolism is related to the inhibition of hair growth and tumor growth, to the development of cutaneous striae of Cushing's disease and to the delay in wound healing "which has been observed in animal and human subjects during administration of these and related hormones." Baker and Whitaker [4] take a different view and show that cortisone causes an impairment of the growth of granulation tissue by local action and not by loss of nitrogen from the body.

Ragan and others [5] noted that in patients under treatment with cortisone and corticotrophin for lupus erythematosus, periarteritis nodosa, and rheumatoid arthritis, there was delay in the healing of the incised wounds and depression of growth of granulations in open wounds. He then compared the rate of healing of skin defects in rabbits' ears under control conditions and with the use of cortisone. After five days the control wounds were covered with granulations and histologically showed profuse growth of all new connective tissue elements—fibroblasts, blood vessels, and ground substance. In the cortisone-treated animals no new granulation had appeared, the blood vessels were exposed, and microscopically there was marked suppression of all elements of connective tissue healing. Spain and others [6] have shown the same general effect of cortisone on wound healing.[7]

In our experiments, pathological specimens were taken from the peritoneal surfaces of the rats when killed at various periods after injection of talc, and histological studies were made. Our pathological findings are in accordance with those found by Ragan [5] and Spain.[6] In the cortisone-treated animals there was little inflammatory reaction, with a decided decrease in ground substance. Granulation

3. Sprague, R. G.; Power, M., and Mason, H. L.: Physiological Effects of Cortisone and ACTH in Man, J. A. M. A. **144**:1341 (Dec. 16) 1950.

4. Baker, B. L., and Whitaker, W. L.: Interference with Wound Healing by the Local Action of Adrenocortical Steroid, Endocrinology **46**:544, 1950.

5. Ragan, C.; Howes, E. L.; Plotz, C. M.; Meyer, C.; Blunt, W. J., and Lattes, R.: The Effect of ACTH and Cortisone on Connective Tissue, Bull. New York Acad. Med. **26**:251, 1950.

6. Spain, D. M.; Molomut, N., and Haber, A.: Effect of Cortisone on the Formation of Granulation Tissue in Mice, Am. J. Path. **26**:710, 1950.

7. Ragan, C.: The Effect of Adrenocorticotrophic Hormone on Rheumatic Arthritis, Am. J. Med. **7**:741, 1949. Spain and others.[6]

tissue, fibroblastic proliferation, new blood vessel formation, and the presence of inflammatory cells, particularly eosinophils, lymphocytes and plasma cells, were at a minimum.

Ragan [5] postulates that the suppression of healing in his series during cortisone and corticotrophin therapy must be a general phenomenon resulting from the action of these hormones on all mesenchymal tissues. As such, it should lessen the formation of adhesions in any part of the body. Stinchfield [8] has used cortisone to prevent joint adhesions following arthroplasty. He also produced delayed callus formation in fractured femurs in rabbits. We have sprinkled talcum powder over the pleural surfaces of the right chest in two dogs; the control animal had massive adhesions, and the other, treated with 20 mg. of cortisone twice daily for 14 days, had scarcely any. This work is being extended. The same result should hold for pericardial adhesions; the formation of keloids should be lessened.

Whether the method will become practical will depend on the difference in dosage between that necessary to prevent adhesions and that which will delay wound healing. The toxic or undesirable effects of cortisone and corticotrophin are "more directly related to the amount of drug given than to the size of the daily dose or duration of treatment" (Bunim [9]). Probably more important is the fact that both of these hormones can mask pain, diminish muscular rigidity and suppress fever and therefore postoperative complications may be overlooked.

Lehman and Boys [10] thought that heparin treatment for three days was sufficient to prevent intra-abdominal adhesions. White,[11] using dicumarol,® also concluded that anticoagulant therapy for four days postoperatively was as effective as that for longer periods. Schiff, Goldberg, and Necheles [1] attempted to keep the bowel surfaces apart by using neostigmine (prostigmine®) injections every four hours for 48 hr. and immediate feeding. They state: "If the fibrinous agglutination of the surfaces can be prevented during the first postoperative days, then the formation of fibrous adhesions will be checked since Hertzler has shown that mesothelium is healed in four to seven days."

From our experiments, apparently it is necessary to give cortisone for at least 10 to 14 days daily to afford the greatest protection against the formation of postoperative adhesions. It is known that in the experimental animal granulation tissue may be found within one hour or so after injury. Administration of cortisone, it would appear, should be started on the day of onset of injury and kept up long enough to prevent the proliferation of fibroblasts; 10 to 14 days apparently is sufficient. These differences as to duration of treatment are probably explained by the difference in the action of cortisone and that of heparin and dicumarol.® Cortisone, it has been shown, delays the formation of granulation tissue, namely, blood vessels, fibroblasts, and ground substance, whereas the action of heparin and dicumarol® is mainly in preventing the formation of fibrin.

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SUMMARY

Cortisone and corticotrophin (ACTH) were effective in considerably reducing the number of intra-abdominal adhesions resulting from talcum powder in experimental animals, dogs and rats. Dosages of 10 mg. of cortisone or 5 mg. of corticotrophin twice daily in the dog and of 2 mg. of cortisone once daily in the rat were sufficient to prevent the formation of adhesions. These dosages did not interfere with wound healing. There was not one single incident of wound dehiscence or of abdominal evisceration. Daily injection of cortisone and corticotrophin for 10 to 14 days appears necessary for the prevention of intra-abdominal adhesions.

ROLE OF CARDIOVASCULAR STRESS IN THE PATHOGENESIS OF ENDOCARDITIS AND GLOMERULONEPHRITIS

Observations Including Method of Experimental Production Utilizing Arteriovenous Fistulas

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MINNEAPOLIS

THE OBSERVATION [1] has been made that dogs with large arteriovenous fistula loads "spontaneously" acquired endocarditis and that in some acute proliferative glomerulonephritis also developed in the period of six weeks to five months following the construction of their arteriovenous shunts. The mechanism of these observations would appear to depend on the fact that the application of a systemic cardiovascular stress, such as large arteriovenous fistulas, causes certain physiological alterations to occur within the dogs, which result in a significant and specific increase in the susceptibility of the endothelial surfaces of the heart and kidneys to bacteria or to the products of bacterial infection. This increase in susceptibility is so great that the animals can acquire their endocarditis from the relatively few microorganisms which gain entrance into their blood streams by adventitious routes. This fortuitous entrance of bacteria through skin or intestinal mucosal abrasions into the blood stream no doubt occurs in most animals from time to time, but under normal conditions no localization occurs since the normal body defenses readily destroy the organisms.

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1. (a) Lillehei, C. W.; Bobb, J. R. R., and Visscher, M. B.: Occurrence of Endocarditis with Valvular Deformities in Dogs with Arteriovenous Fistulae, Proc. Soc. Exper. Biol. & Med. **75**:9-16, 1950; (*b*) The Occurrence of Endocarditis with Valvular Deformities in Dogs with Arteriovenous Fistulas, Ann. Surg. **132**:577-590, 1950.

2. Footnote deleted.

On the basis of these initial observations an experimental method has been developed for the production of endocarditis and diffuse proliferative glomerulonephritis [3] in dogs. This method (Fig. 1) utilizes the cardiovascular stress of bilateral arteriovenous fistulas in the lower extremities plus bacteremia produced by the intravenous injections of small doses of bacteria. The use of this method, as portrayed in Figure 1, has several advantages. First, the occurrence of endocarditis can be increased to 100% from the 70% incidence observed when the endocarditis occurred "spontaneously" in dogs with large arteriovenous shunts; secondly, the time interval required is reduced to a matter of days from the six-week to five-month period required for the spontaneous occurrence of endocarditis, and, finally, the relatively small numbers of bacteria required for injection into dogs with bilateral arteriovenous fistulas in order to produce endocarditis by this method serves to emphasize the profound effect of systemic stress on the susceptibility to infection of the heart and kidney endothelium. This concept, we believe, has considerable

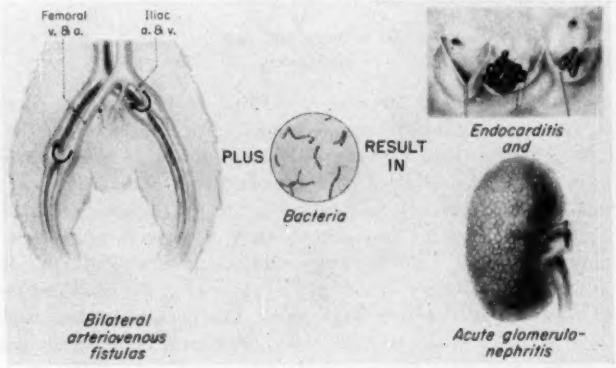

Fig. 1.—Method for the experimental production of endocarditis with valvular deformities and glomerulonephritis (in dogs).

potential clinical significance in relationship to a more complete understanding of human resistance and susceptibility to infection.

PLAN OF EXPERIMENTS

The present studies extend the initial observations, which indicated that a wide difference exists in susceptibility of the endothelium of the heart and kidneys to infection between normal dogs and animals with an appreciable cardiovascular stress such as that created by bilateral arteriovenous fistulas in the lower extremities.

In addition, susceptibility to infection has been studied in a group of animals subjected to a smaller degree of cardiovascular stress, such as occurs with a single

3. Lillehei, C. W.; Bobb, J. R. R.; Wargo, D.; Visscher, M. B.; Shaffer, J. M., and Bell, E. T.: Experimental Production of Diffuse Proliferative Glomerulonephritis Utilizing Arteriovenous Fistulas and Bacteremia, Circulation, to be published.

short femoral arteriovenous shunt. In this group of animals, the degree of susceptibility to infection has been studied by creating a bacteremia in the following two ways: (1) by injecting bacteria in doses more than sufficient to give a 100% incidence of endocarditis in the dogs with a greater systemic stress (bilateral shunts) and (2) by injection of bacteria into dogs whose arteriovenous shunt is only a few days old with the expectation that the bacteria will localize and multiply in the locus minoris resistentiae of the recent operative site and in this way create a continuous bacteremia. Such experiments should be expected to provide a crucial test of the relative importance of systemic stress compared to the simple presence of bacteremia in localizing the bacteriological invasion to the endothelium of the heart valve leaflets and the kidney glomeruli.

METHOD OF STUDY

The animals used in these studies were young adult dogs, of medium size and of both sexes, previously dewormed, immunized against distemper, dipped in a parasiticide,[4] and acclimated to the animal colony for a period of four weeks before use. All dogs were fed daily a diet consisting of standard dog biscuits supplemented with fresh horsemeat and crude cod liver oil.

We should like to emphasize that for experiments of this nature involving stress and infection it is of the utmost importance for consistent results to utilize animals in the best possible physical condition.

Group I. Dogs with a Large Arteriovenous Fistula Load (Table 1).—The bilateral arteriovenous shunts in this group of animals were made side-to-side 15 to 32 mm. in length between the iliac and femoral arteries and veins, respectively, as indicated in Figure 1. These shunts were constructed in stages usually a week or more apart. Penicillin-in-oil (300,000 units each day) was given to each animal every day for one week after each surgical procedure. A recovery period of at least two weeks was allowed for all animals after the last surgical procedure for complete healing of the operative wounds and for the compensatory changes of the arteriovenous fistulas to take place before the intravenous injections of beta hemolytic streptococci[5] (Lancefield Group D) were begun. The dose of bacteria given to the dogs in this group varied from 0.05 to 0.5 ml. per day of a 24-hr. broth culture for a period of seven to 10 consecutive days. The average colony count on a 24-hr. broth culture of this organism was 1,500,000,000 bacteria per milliliter.

Group II. Dogs with a Small Arteriovenous Fistula Load (Table 2).—A single femoral arteriovenous fistula 10 to 11mm. in length was constructed in each dog of this group. The postoperative recovery period before bacterial injections were begun was intentionally varied, as indicated in Table 2, from four to 30 days in order to assay the relative importance of varying durations of a small increase in cardiovascular stress in localizing the pathological involvement to the heart valves and kidney glomeruli. Also, it was anticipated that when there was a very short interval between construction of the arteriovenous shunts and the intravenous injection of bacteria the animals might acquire an infection at their fistula site, and the consequent continuous bacteremia plus a definite but small increase in cardiovascular stress (from the single femoral arteriovenous fistula) would provide a test of the relative importance of these two factors in localizing bacterial involvement to the valve leaflets and kidneys. All the dogs in this group were given a daily intravenous dose of 0.5 ml. of hemolytic streptococci[5] (Lancefield Group D) for seven consecutive days.

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4. Vermiplex® (Pittman-Moore Co., Division of Allied Laboratories, Inc., Indianapolis) was used for the deworming, virogen® (same company) for the distemper, and "lexone" (E. I. DuPont de Nemours & Co., Wilmington, Del.) for the parasiticide.

5. "Strain, I. F."

Group III. Normal Dogs (Table 3).—This group consists of normal control animals similar in all respects to those in Groups I and II, except for the absence of arteriovenous fistulas. All these normal animals received a daily intravenous dose of this same [5] strain of Group D hemolytic streptococci [5] varying from 0.5 cc. to 50.0 ml. for six or seven consecutive days.

In all dogs with arteriovenous fistulas a negative blood culture was obtained before bacterial injections were begun. This precaution is essential because an occasional animal with bilateral arteriovenous shunts will be found to have acquired spontaneous endocarditis during even a short postoperative interim.

Rectal temperatures and pulse rate determinations were taken daily during the preoperative control period and after the construction of arteriovenous shunts. In the postoperative interval, daily auscultation of the fistulas and the hearts was added to the routine to ascertain if the former were open and to detect the time of onset of systolic and diastolic murmurs associated with the occurrence of serious valvular defects in the heart. Six-foot roentgenograms of the heart were made in all animals when they were normal, at the time bacterial injections were commenced, and also at appropriate intervals before death. The frontal area of the cardiac silhouette was measured by use of a compensating polar planimeter. This method has a technical error [6] of less than 2%. The amount of cardiac enlargement was intended to serve as a simple gross index of the degree of cardiovascular stress created by the arteriovenous shunts.

Bacteriological Data.—Several different strains and several different species of bacteria have been successfully used for the production of endocarditis by this method. The bacterial strain used in all the experiments herein reported was originally chosen at random from a hospital laboratory and has been identified as a Lancefield Group D strain of hemolytic Streptococcus with the beta type of hemolysis. This organism, which we have named "strain I. F.," was isolated from a patient [7] with cholangitis and hepatic abscesses due to malignant obstruction of the common bile duct. A 24-hr. culture in tryptose phosphate broth was used for all injections. Colony counts upon such a 24-hr. broth culture of this organism were performed once a week to give a rough measure of the number of organisms being injected. These colony counts indicated that from day to day the number of organisms per milliliter of a 24-hr. broth culture averaged 1,500,000,000, with a range from 1,290,000,000 to 2,450,000,000.

All the bacterial injections in this series of dogs were made intravenously with the use of sterile syringes and preparation of the skin as indicated below. A 0.05 ml. dose of a 24-hr. culture was made by injecting 0.5 ml. of a 1 : 10 dilution of the 24-hr. broth culture using isotonic sodium chloride solution as the diluent. Blood cultures were made at frequent intervals by withdrawing 10 ml. of blood from the jugular vein into a sterile syringe after preparation of the skin, which consisted in shaving off the hair, cleansing with soap and water, and then applying benzalkonium chloride (tincture zephiran chloride,® 1 : 1,000). One-half of this blood was placed in broth and the other half into 3.5% sodium citrate solution for use in making pour plates for colony counts. The number of organisms per milliliter of blood was roughly quantitated for all positive cultures by the usual dilution methods. The organism used in these experiments was tested for sensitivity to penicillin, aureomycin and streptomycin and was found to be inhibited in vitro by the following concentration of antibiotics: penicillin, 1.9 units; aureomycin, 7.8 micrograms; streptomycin, 62.5 micrograms; penicillin plus aureomycin, 1.9 units or micrograms of each drug, and penicillin plus streptomycin, 3.9 units or micrograms of each drug per milliliter.

RESULTS

In the dogs of Group I, with large bilateral arteriovenous fistulas of the size and position indicated in Figure 1, the degree of cardiovascular stress existing at the time bacterial injections were begun was indicated by the enlargement of their car-

6. The inherent error of measuring three dimensional figures by the use of only two dimensions is recognized.

7. I. F., U. H. No. 817510.

diac frontal areas varying from 19 to 101% as compared to their normal cardiac silhouette (Table1). The daily intravenous injection of 0.05 to 0.5 ml.[8] of a 24-hr. broth culture of a beta hemolytic Streptococcus (Lancefield Group D, "Strain I. F.") for seven to 10 days resulted in endocarditis in all these dogs. Acute diffuse pro-

TABLE 1.—*Production of Endocarditis in Dogs with Bilateral Arteriovenous Fistulas Receiving Injection of Beta Hemolytic Streptococcus (Group D)*

		Arteriovenous Fistulas			Cardiac Frontal Area			Intravenous Dose of 24 Hr. Broth Culture*			Survival from Start of Bacterial Injections, Days		
Dog No.	Sex and Weight, Lb.	Location	Length, Mm.	Duration at Start of Bacterial Injection, Days	Normal, CM.²	At Start of Bacterial Injection, CM.²	Increase, %	Ml./Day	No. of Days	Result		Cause of Death	Heart Valves Involved
56	M 35	Iliac, femoral	23 17	137 14	64.0	79.7	24.5	0.05	7	Died	61	Endocarditis	Mitral, aortic
718	M 32	Iliac, femoral	32 21	17 14	67.6	....	....	0.5	10	Died	17	Endocarditis	Mitral, tricuspid
70	M 60	Iliac, femoral	29 25	286 20	89.1	179.1	101.0	0.5	7	Died	15	Endocarditis Glomerulonephritis	Mitral, tricuspid
100-x	M 50	Iliac, femoral	30 15	278 142	94.4	145.7	54.3	0.5	7	Died	25	Endocarditis Glomerulonephritis	Mitral, aortic and tricuspid
1886	F 38	Iliac, femoral	25 20	22 76	70.1	83.6	19.1	0.5	7	Died	48	Endocarditis	Mitral, aortic

Number of dogs with arteriovenous fistulas injected = 5
Number of dogs with endocarditis = 5
Number of dogs with glomerulonephritis = 2
* Average colony count per milliliter of 24-hr. broth culture of beta hemolytic Streptococcus (Group D, "Strain I. F.") = 1,500,000,000.

TABLE 2.—*Results of Bacterial Injection (Beta Hemolytic Streptococcus, Group D) into Dogs with a Single Small Femoral Arteriovenous Fistula*

	Arteriovenous Fistulas			Heart Size			Dose of 24-Hr. Broth Culture*			
Dog No.	Location	Length, Mm.	Duration at Start of Bacterial Injection, Days	Normal, Cm.²	At Start of Bacterial Injection, Cm.²	Increase, %	Ml./Day	No. of Days	Result	Comment
120	Femoral	10	4	51.0	56.3	10.3	0.5	7	Killed	No endocarditis No glomerulonephritis
1918	Femoral	10	6	48.4	50.6	4.5	0.5	7	Killed	No endocarditis No glomerulonephritis
119	Femoral	10	9	52.8	53.3	None	0.5	7	Killed	No endocarditis No glomerulonephritis
814	Femoral	11	30	81.1	80.3	None	0.5	7	Killed	No endocarditis No glomerulonephritis

Number of dogs with single femoral arteriovenous fistula injected = 4.
Number of dogs with single femoral arteriovenous fistula with endocarditis or glomerulonephritis = 0.
* Average colony count per milliliter of a 24-hr. broth culture of beta hemolytic Streptococcus (Group D, "Strain I. F.") = 1,500,000,000.

liferative glomerulonephritis also occurred in two of five of the animals (Table 1). In these experiments the occurrence of glomerulonephritis is noted for completeness. A more detailed pathological description together with a discussion of the kidney lesions is presented in a separate publication.[3] All the dogs in this series died. Death was due to a combination of one or more of the following factors: the

8. 1,500,000,000 organisms per milliliter.

overwhelming bacteremia that develops in these animals, the occurrence of severe destructive lesions of their heart valves from the formation of vegetations, and the development of glomerulonephritis.

The mitral valve leaflets were involved by vegetations in all five of these dogs. In addition, the aortic and tricuspid valves were each involved in three of the five animals. However, the severest lesions generally occurred on either the mitral or the aortic valves. Also, one animal (100-x) had involvement of all three valves. The pulmonary valve was uninvolved in all animals. Grossly and microscopically the valvular vegetations were of two distinct types, bacterial-like and rheumatic-like. A gross description of these lesions has been presented.[1] The microscopic analysis will be presented later.[9] Table 1 indicates the valves on which gross lesions were found. A brief record of the gross pathological finding in these five dogs follows.

TABLE 3.—*Bacterial Injection (Beta Hemolytic Streptococcus, Group D) into Normal Control Dogs*

Dog No.	Intravenous Dose of 24 Hr. Broth Culture,* Ml./Day	No. of Days	Total Intravenous Bacteria Dose† (24-Hr. Broth Culture), Ml.	Result	Comment
1162	0.5	7	3.5	Killed	No endocarditis No glomerulonephritis
198	2.0	7	14.0	Killed	No endocarditis No glomerulonephritis
1887	0.5	7	3.5	Killed	No endocarditis
	2.0‡	7	14.0		No glomerulonephritis
			17.5		
386	50.0	6	300.0	Killed	No endocarditis No glomerulonephritis
277	50.0	7	350.0	Killed	No endocarditis No glomerulonephritis
294	50.0	7	350.0	Killed	No endocarditis No glomerulonephritis

Number of normal dogs injected = 6.
Number of dogs with endocarditis or glomerulonephritis = 0.

* Average colony counts on 24-hr. broth culture of beta hemolytic Streptococcus (Group D, "Strain I. F.") = 1,500,000,000 organisms per milliliter.

† Total dose = daily dose of 24-hr. broth culture in milliliters multiplied by number of days of injection.

‡ Twenty-six day interval between the two series of injections.

Dog 56.—At autopsy there was moderate edema of the right hindleg and thigh. There was no hydrothorax or ascites, and there was massive pulmonary edema of all lobes. The pulmonary valve was normal. The tricuspid valve showed some edema of the septal leaflet but was otherwas normal. The aortic valve had two large soft friable vegetations (4 by 2 by 1.5 mm. each) destroying two of the three cusps. The mitral valve was diffusely thickened, with a number of small smooth hard nodules along the edge of the leaflets. The first portion of the aortic intima showed nine hard nodular projections just distal to the aortic valve. Both iliac and femoral arteriovenous fistulas were open, with no vegetations.

Dog 718.—At autopsy bloody froth about the nostrils and filling the trachea was noted. There was no peripheral edema, no hydrothorax and no ascites, but massive pulmonary edema of all lobes. The aortic and pulmonary valves were normal. The mitral valve was replaced by a large (3 by 2.5 by 1.5 cm.) soft friable verrucous vegetation, with a number of tiny subendothelial

9. Lillehei, C. W.; Bobb, J. R. R.; Visscher, M. B., and Clawson, B. J.: A. Study of the Pathological Lesions Occurring in Experimental Endocarditis Produced by Arteriovenous Fistulas, to be published.

Fig. 2.—Bottom picture, Dog 100-x with mitral valve endocarditis (mitral valve viewed from above looking into the opened left atrium.) Note white marker inserted through the small valve orifice (mitral stenosis) completely surrounded by the large verrucous vegetations projecting upward into the left atrium (due to a mitral regurgitation). Compare with a normal mitral valve in Figure 3*a*. Top picture, Dog 1886, with aortic valve endocarditis. Note that two of the cusps of the valve are completely destroyed by large vegetations. The third cusp (on the right) is thickened and has several smaller vegetations on its surface. Compare with a normal aortic valve in Figure 3*B*.

hemorrhages seen over the remainder of this valve. The tricuspid valve showed a single definite soft wartlike vegetation (1.5 by 2 by 3 mm.). Both iliac and femoral arteriovenous fistulas were open and contained vegetations along their margins similar to those seen on the mitral valve.

Dog 70.—Autopsy showed much bloody frothy fluid filling the trachea and running out of the nostrils. There was no peripheral edema, hydrothorax, or ascites. There was massive pulmonary edema of all lobes. The aortic and pulmonary valves were normal. The mitral valve was diffusely thickened, with several moderately large (0.5 by 1.0 by 1.0 cm.) soft friable bacterial-like vegetations. The edges of the rest of the leaflets were lined by small, firm rheumatic-like nodules. The tricuspid valve had rheumatic-like nodules along the leaflet margins. Both femoral and iliac fistulas were open and clean.

TABLE 4.—*Results of Blood Cultures in Dogs Given Injections of Beta Hemolytic Streptococci (Group D)**

Dog No.	Amount of Cardiovascular Stress	Total Intravenous Bacteria Dose† (24-Hr. Broth Culture), Ml.	Dates of Bacteria Injections	Results of Blood Cultures: Date	Results of Blood Cultures: No. of Organisms/Ml. of Blood (Beta Streptococci)	Comment, Therapy
56	Iliac, femoral arteriovenous fistula	0.35	7/22-7/28 (inc.)	7/21	Negative	None
				8/3	87	
				8/15	6740	
				8/23	405	
						9/20 Died
718	Iliac, femoral arteriovenous fistula	5.0	5/9-5/18 (inc.)	5/19	1284	None
				5/25	7000	
						5/25 Died
70	Iliac, femoral arteriovenous fistula	3.5	1/3-1/9 (inc.)	1/2	Negative	1/16 to death received a daily dose of 800,000 units of penicillin and 1.5 gm. of aureomycin
				1/11	27	
				1/12	639	
				1/18‡	1457	
						1/18 Died
100-x	Iliac, femoral arteriovenous fistula	3.5	12/13-12/19 (inc.)	12/22	2102	1/4 to death received a daily dose of 700,000 units of penicillin and 1.5 gm. of aureomycin
				12/23	5040	
				1/2	3148	
				1/5‡	2656	
						1/16 Died
1886	Iliac, femoral arteriovenous fistula	3.5	1/3-1/9 (inc.)	1/2	Negative	1/19-2/5 (inc.) received a daily dose of 1,500,000 units of penicillin, 1.5 gm. of aureomycin and 1.0 gm. of streptomycin
				1/11	1402	
				1/12	930	
				1/18	1085	
				1/23‡	760	1/29 both arteriovenous fistulas taken down surgically
				1/29‡	274	
				2/1‡	Negative	2/16 to death received same dose of antibiotics as above
				2/3‡	4	
				2/6	13	
				2/9	124	
				2/13	1440	
				2/16‡	78	
						2/20 Died

* Average colony count on a 24-hr. broth culture of this organism ("Strain I. F.") = 1,500,000,000 bacteria per milliliter.

† Total bacteria dose = daily dose of a 24-hr. broth culture in milliliters multiplied by the number of days of injection.

‡ Animal receiving antibiotic therapy at time culture was made.

Dog 100-x.—At autopsy the trachea was full of bloody frothy fluid. There was massive pulmonary edema of all lobes. Bilateral hydrothorax was present but no ascites. There were multiple petechial hemorrhages in the adrenal cortices. The pulmonary valve was normal. The aortic valve had multiple soft friable vegetations approximately 5 mm. in diameter adherent to all three cusps. On the mitral valve the entire surface area of these leaflets was covered by large (2 to 3 cm.) verrucous bacterial-like vegetations projecting upward into the left atrium (Fig. 2, lower picture). The tricuspid valve had a number of small hard rheumatic-like nodules along the leaflet margins. The normal trifurcation of the distal aorta was surrounded by a ring of bacterial-like vegetations. The iliac arteriovenous fistula was open and had several (3 by 4 mm.) bacterial-like vegetations along the margins. The femoral arteriovenous fistula was open and free of vegetations.

Dog 1886.—Autopsy showed severe pulmonary edema of all lobes. The pulmonary and tricuspid valves were normal. The mitral valve had several hemorrhages plus a few small rheumatic-like nodules along the margins. In the aortic valve two of the three cusps were completely destroyed by large soft vegetations. The third cusp was covered with smaller vegetations and considerably thickened (Fig. 2, upper picture). The arteriovenous fistulas had previously been excised surgically.

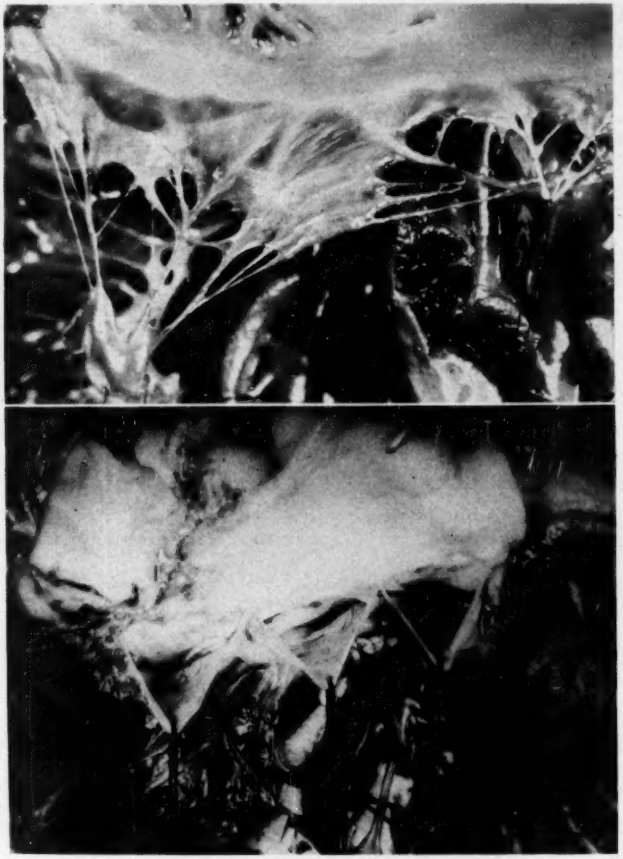

Fig. 3.—Normal heart valves for comparison. Note tissue-paper thinness of normal leaflets. *A*, mitral valve; *B*, aortic valve.

In two (Dogs 56 and 718) of the five animals in Group I (Table 1) no therapeutic efforts were made to keep the animals alive after the establishment of their endocarditis. These two animals died 61 and 17 days, respectively, after the time bacterial injections were begun. This result is in agreement with previously pub-

lished results.[10] The blood cultures in these animals became positive shortly after the conclusion of the bacterial injections and remained consistently positive until their death. The number of organisms per milliliter of blood rose as high as 7,000 in these dogs, as indicated in Table 4. In the three other dogs in this group an effort was made to cure the endocarditis after its establishment. Two of the dogs (Nos. 70, 100-x) received large doses of penicillin (700,000 to 800,000 units per day) by injection and 1.5 gm. of aureomycin (in divided oral doses) daily, without any apparent effect on the course of their endocarditis. Antibiotic treatment in these dogs was begun 13 and 22 days, respectively, after their first bacterial injection, and they lived a total of 15 and 25 days from the date of the first bacteria injections. In the fifth dog (No. 1886) a determined therapeutic effort was made utilizing large doses of antibiotics beginning 16 days after the first bacterial injection,

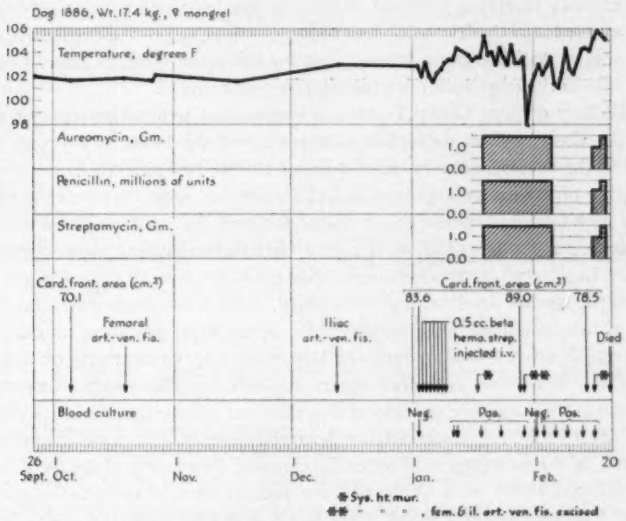

Fig. 4.—Clinical course and therapy of endocarditis in Dog 1886, a female mongrel weighing 17.4 kg.

together with excision of both arteriovenous fistulas on the 26th day after the onset of endocarditis. By these methods it was possible to sterilize the blood stream in this dog temporarily, but the bacteremia reappeared even though continuous antibiotic therapy consisting of aureomycin (1.5 gm. per day orally in divided doses) and penicillin (1,500,000 units per day by intravenous and intramuscular injection) and streptomycin (1.0 gm. per day in divided doses by injection) was being maintained. This dose of antibiotics was given for a total of 23 days, as indicated in Figure 4. The dog lived a total of 48 days from the onset of the endocarditis, and although it seems likely that the duration of life was prolonged by this intensive therapy, death eventually occurred from a combination of the Streptococcus bac-

10. Footnotes 1 and 3.

teremia and a severe destructive lesion of the aortic valve (Fig. 2, upper picture) together with rheumatic-like vegetations on the mitral leaflet.

The results of the injection of this same strain of bacteria into normal dogs is in distinct contrast to the results observed in dogs with bilateral arteriovenous fistulas. In these normal dogs, the daily intravenous injection of from 0.5 to 50.0 milliliters of a 24-hr. broth culture [11] for six or seven days caused no apparent ill effects except transient fever. All the animals remained in excellent health, and it was necessary to kill them for autopsy. The results are summarized in Table 3. Neither endocarditis nor glomerulonephritis was found. The blood cultures in these animals revealed a low-grade bacteremia nearly always (one to two organisms per milliliter of blood) for the first one or two days immediately after the cessation of a course of bacterial injections. However, after this short interval the blood streams again became sterile in all cases. A detailed analysis of the blood culture data on these normal animals receiving bacterial injections has been presented elsewhere.[3] It should be noted also that the total dose of bacteria injected into these normal control animals was up to 1,000 times greater than the minimum dose necessary to produce endocarditis in the dogs with bilateral arteriovenous shunts.

Of the four dogs of Group II, with a single short femoral arteriovenous shunt (Table 2), there was no detectable enlargement of the heart in two and a slight increase in the cardiac frontal area of 4.5 and 10.3%, respectively, in the other two. This degree of cardiac enlargement is to be compared with the results observed in the dogs with bilateral arteriovenous shunts in which the cardiac silhouette was 19.1 to 101% larger than normal at the time bacterial injections were begun. It is altogether likely that an appreciable cardiac dilatation occurs only when a critical increment in cardiac load has been exceeded. The daily intravenous injection of 0.5 ml. of beta hemolytic streptococcus [5] for seven days into these animals with a single femoral arteriovenous shunt did not cause any endocarditis or glomerulonephritis, nor were there any other apparent ill effects. This result is in direct contrast to the 100% incidence of endocarditis that was observed in the dogs with large bilateral arteriovenous fistulas after a bacterial dose of the same magnitude. As anticipated, in the two dogs with femoral fistulas of only four and six days' duration (Dogs 120 and 1918) it is likely that the fistulas became the site of a localized infection. This conclusion is based on the fact that in both animals the blood cultures indicated a significant but transient elevation (up to 24 organisms per milliliter of blood in Dog 120 and up to 381 organisms in Dog 1918) above the usual degree of bacteremia. Nevertheless, even in the presence of this temporary septicemia, there was no tendency for the bacterial infection to involve the endothelium of the heart or kidneys and the bacteremia spontaneously disappeared. A detailed analysis of the results of the blood cultures in this group of animals has also been presented elsewhere.[3]

COMMENT

By utilizing the cardiovascular stress of bilateral arteriovenous fistulas in the lower extremities of dogs together with transient bacteremia produced by daily intravenous injections of from 0.05 to 0.5 ml. of a 24-hour broth culture of beta hemolytic Streptococcus [5] (Group D) for 10 days or less, endocarditis was produced

11. Average colony count, 1,500,000,000 organisms per milliliter.

in 100% of the animals. Acute diffuse proliferative glomerulonephritis also occurred in 40%. This finding is in agreement with our previously published results [12] indicating that dogs with large arteriovenous fistulas are unusually susceptible to bacterial involvement of their heart valves and kidney glomeruli.

In normal dogs the intravenous injection of doses of the same bacteria up to one thousand times the dose necessary to produce endocarditis in animals with arteriovenous shunts did not cause endocarditis or glomerulonephritis (Table 5). Studies now in progress indicate that the minimum dose of bacteria necessary to cause endocarditis in 100% of dogs with large arteriovenous fistula loads can probably be increased more than 10,000 times in normal dogs, without the observance of either endocarditis or glomerulonephritis. These findings are a striking demonstration of the effect of a systemic cardiovascular stress in promoting infection of the heart valves and the kidney endothelium.

The difficulties of attempting to produce endocarditis or glomerulonephritis by bacterial injection alone in normal animals, particularly the dog, has been previously documented by a number of investigators. Kinsella and Muether [13] were unable to

TABLE 5.—*Relationship of Cardiovascular Stress and Increased Susceptibility to Bacterial Infection (Beta Hemolytic Streptococcus, Group D, "Strain I. F.")*

Amount of Cardiovascular Stress	No. of Dogs	Total Intravenous Bacteria Dose* (24-Hr. Broth Culture), Ml.	Result
Bilateral (iliac and femoral) arteriovenous fistulas	5	0.35 to 5.0	Endocarditis developed in 100% Glomerulonephritis developed in 40% All animals died
Single short femoral arteriovenous fistula	4	3.5	No endocarditis No glomerulonephritis
Normal dogs	6	3.5 to 350.0	No endocarditis No glomerulonephritis

* Total dose = daily dose (in milliliters) of a 24-hr. broth culture of beta hemolytic Streptococcus multiplied by the number of days of injection.

produce endocarditis in dogs by injecting streptococci. Dick and Schwartz [14] were able to produce endocarditis in approximately 30% of 83 dogs only by continually injecting doses of up to 100 cc. of broth cultures of streptococci intravenously four times weekly for varying periods up to six and three-quarter years. Likewise, we [3] have recently reviewed briefly in another publication the difficulties recorded by earlier investigators in attempting experimentally to produce diffuse proliferative glomerulonephritis by injection of bacteria or their toxins.

In the group of dogs with a single short femoral arteriovenous shunt, there was, as indicated, a small but definite increase in the cardiovascular stress, yet injection of numbers of bacteria well within the range followed by endocarditis with bilateral shunts did not produce any demonstrable lesions. Furthermore, even in the presence of appreciable septicemia associated with an infected fistula site, there was still no involvement of the heart valves or kidneys. We believe that this finding adds further

12. Lillehei and others.[1]

13. Kinsella, R. A., and Muether, R. O.: Experimental Streptococcic Endocarditis, Arch. Int. Med. **62**:247-270 (Aug.) 1938.

14. Dick, G. F., and Schwartz, W. B.: Experimental Endocarditis of Dogs, Arch. Path. **42**:159-162 (Aug.) 1946.

support to our contention, suggested in an earlier publication,[1a] that the primary factor in the susceptibility to endocardial infection is the cardiovascular stress and, further, that this systemic stress must be of sufficient degree before the resultant changes in endothelial susceptibility to infection are evident.

These significant differences in resistance to infection in relationship to cardiovascular stress are summarized in Table 5 and represent the factual data serving to emphasize the thesis stated initially that the application of a systemic cardiovascular stress is associated with certain physiological alterations [15] within the organism which together result in a significant and specific increase in the susceptibility of the endothelial surfaces of the heart and kidneys to bacterial infection or its products.

The relative ineffectiveness of penicillin and the other antibiotics aureomycin and streptomycin in the treatment of this endocarditis and glomerulonephritis is noteworthy. In this regard, the ineffectiveness of the antibiotics in the therapy of some of the sequelae of streptococcus infections such as glomerulonephritis and rheumatic fever has been noted clinically.[16] However, it should be mentioned that the observations made on the use of antibiotics in these experiments are preliminary in nature. It should be noted that the particular strain of beta hemolytic Streptococcus that we happened to have chosen for the experiments was moderately resistant to all three of the antibiotics used. Also, the therapeutic effects of the antibiotics would in all probability be enhanced by still further shortening of the interval between the onset of endocarditis and the beginning of therapy.

Having demonstrated experimentally that systemic cardiovascular stress is associated with a specific increase in susceptibility to infection of certain endothelial surfaces, one might logically inquire what clinical significance this relationship may have. First, it can be said that a similar specific loss of resistance to infection of the heart valves and kidneys can occur in human beings exposed to cardiovascular stress. We [17] have collected a series of cases from the literature in which endocarditis and glomerulonephritis were observed to have occurred as complications of untreated acquired arteriovenous fistulas.

Of greater practical importance, perhaps, is the question of whether these same mechanisms might not account for certain pathological aspects of congenital heart disease. The association of congenital heart lesions with a high incidence of bacterial endocarditis has been recognized for many years. The mechanisms demonstrated here experimentally provide an apparently adequate basis for the explanation of this observed increased susceptibility to infection. Moreover, there exists another large group of patients with congenital heart disease, particularly septal defects with arteriovenous shunts, who die from heart failure due to acquired chronic valvular heart disease. The high incidence of acquired chronic valvular heart lesions associated with congenital heart disease, particularly with interatrial and interventricular

15. Lillehei, C. W.; Bobb, J. R. R., and Visscher, M. B.: Effect of Arteriovenous Fistulas upon Pulmonary Arterial Pressure, Cardiac Index, Blood Volume, and the Extracellular Fluid Space, in American College of Surgeons, Surgical Forum, Philadelphia, W. B. Saunders Company, 1951, pp. 275-282.

16. Swift, H. F.: Bacterial and Mycotic Infections of Man, edited by R. J. Dubos, Philadelphia, J. B. Lippincott Company, 1948, p. 274.

17. Lillehei, C. W.: The Occurrence in Man of Endocarditis and Glomerulonephritis as a Complication of Acquired Arteriovenous Fistulas, to be published.

septal defects, and patent ductus, all lesions which have arteriovenous shunts, has been the subject of discussion by a number of authorities.[18] It seems possible that these deformed valves are acquired as the result of one or more attacks of endocarditis engendered by the increased susceptibility associated with the cardiovascular stress of their arteriovenous shunt.

The observations herein reported may also contribute to an elucidation of the mechanism of production of bacterial endocarditis in patients with acquired valvular heart disease. It is generally stated that the damaged or scarred rheumatic valve represents a locus minoris resistentiae and that subsequent infections localize in the heart valves for this reason. It is doubtful that this simple explanation is adequate. In view of the findings in the arteriovenous shunt dogs, it seems more likely that the cardiovascular stress created by the presence of an incompetently functioning heart valve due to the prior scarring produces a state of increased susceptibility to infection. We think that the clinical course of Dog 1886 (Fig. 4) supports this suggestion. Once the endocarditis in this animal was so well established on the aortic valve that the function of this valve was seriously impaired, it was impossible to eradicate the endocarditis even by excision of both fistulas. By this time the leaking heart valve was a sufficient stress, as manifested by the enlarged heart size, to maintain the increased susceptibility. As has been suggested in a previous publication,[1b] the inherent self-perpetuating characteristics of clinical endocarditis which make therapy so difficult may well be based on these same phenomena.

Obviously, it will be of considerable importance to define exactly what changes associated with cardiovascular stress are responsible for this altered response to bacterial infection. Further studies are in progress. It seems likely that mechanical factors set in motion secondary physiological reactions, such as the adrenal hypertrophy which has been reported,[1] which determine the end result.

SUMMARY

A new experimental method has been presented for the production of endocarditis and glomerulonephritis, utilizing the systemic stress of large arteriovenous fistulas and the injection of small doses of bacteria. The implications of these experimental studies in the pathogenesis of certain forms of acquired and congenital human heart disease are suggested.

CONCLUSION

The application of a systemic cardiovascular stress such as large arteriovenous fistula loads causes a significant and specific increase in susceptibility to bacterial infection of the endothelial surfaces of the heart and kidneys.

DISCUSSION

DR. WILLIS J. POTTS, Chicago: This paper by Drs. Lillehei, Visscher and Bobb has been very interesting. Original work previously reported is such a fundamental contribution to our knowledge of heart disease that I should like to call attention to it again. The authors made arteriovenous aneurysms to study the effect of increased work on the heart and by chance found endocarditis in a large percentage of cases.

18. Abbott, M. E.: Atlas of Congenital Heart Disease, Analysis of 1,000 Cases, New York, American Heart Association, 1936. Roesler, H.: Interatrial Septal Defect, Arch. Int. Med. **54**:339-380 (Sept.) 1934. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, Division of Publications, 1947, pp. 354 and 372.

Instead of further commenting on that work it seems appropriate to point out the fundamental reason for those discoveries, which involves a short discussion of semantics. A relatively uncommon word is applicable to the original work of Lillehei and his associates. The word is serendipity. Walpole wrote a story of the "Three Princes of Serendip." These men wandered about the country with a definite objective in mind but were constantly on the alert for unexpected and unanticipated findings. Slowly the word serendipity has crept into usage and is now defined as a chance discovery unrelated to that for which search was instituted.

There are innumerable examples of such discoveries in all branches of science. The best and most recent example is the monumental discovery of penicillin by Fleming. In his bacteriological researches he was annoyed by the invasion of the mold Penicillium notatum in his agar plates. This great prince of Serendip suddenly by chance saw the hidden power of the growth-inhibiting mold, and today we have penicillin and a host of related antibiotics.

Dr. Lillehei and his co-workers sought information on heart strain by making arteriovenous aneurysms and found endocarditis. Upon serendipity depends future great advances in medicine. The mythical land of Serendip is open to all without visé.

FEMORAL ARTERIOVENOUS ANASTOMOSIS IN THE TREATMENT OF OCCLUSIVE ARTERIAL DISEASE

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DETROIT

THE ULTIMATE theoretical aim of a surgically created femoral arteriovenous anastomosis in the treatment of peripheral obliterative arterial disease is to provide an unobstructed system of vascular channels for the transportation of arterial blood by substituting the venous vascular bed for the diseased arterial tree distal to the shunt through the diversion of the arterial blood into the venous pathways of the limb.

This concept is old, and from 1881 to 1916 its practical applicability was extensively investigated both clinically [1] and experimentally.[2] After 1916 the operation

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From the Department of Surgery of the Henry Ford Hospital.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1951.

1. (*a*) Francois-Franck: Note à propos de la communication de M. Raymond Petit sur la suture artério-veineuse, Compt. rend. Soc. biol. **10**:150, 1896. (*b*) Petit, R.: Note sur la suture et l'anastomose des artères et des veines, Compt. rend. Soc. biol. **10**:79-81, 1896. (*c*) San Mártin y Satrustegui, A. F.: Anastomosis arterio-venosa: Cirugía del aparato circulatorio, Jurado med. -farm. **12**:164-165, 1902; abstracted, Fortschr. Geb. Chir. **8**:218, 1903. (*d*) Carrel, A., and Guthrie, C. C.: The Reversal of the Circulation in a Limb, Ann. Surg. **43**:203-215, 1906. (*e*) Wieting, J.: Die erfolgreiche Behandlung der angiosklerotischen Ernährungsstörungen durch die arteriovenöse Anastomose, Deutsche Ztschr. Chir. **119**:515-551, 1912. (*f*) Bernheim, B. M.: Arteriovenous Anastomosis: Reversal of Circulation as a Preventive of Gangrene of the Extremities: Review of the Literature and Report of 6 Additional Cases, Ann. Surg. **55**:195-207, 1912. (*g*) Goodman, C.: Arteriovenous Anastomosis of the Femoral Vessels for Impending Gangrene, ibid. **60**:62-87, 1914. (*h*) Thomson, A.: Discussion of Freeman's Paper, Tr. Am. S. A. **31**:257, 1913. (*i*) Lilienthal, H.: Arteriovenous Anastomosis for Thrombo-Angiitis Obliterans, ibid. **58**:303-308, 1914. (*j*) Deal, D. W.: Arterio-Venous Anastomosis in the Upper Extremities for Impending Gangrene, Railway S. J. **21**:115-119, 1914-1915. (*k*) Putnam, C. R. L.: Arteriovenous Anastomosis for Thromboangiitis Obliterans, M. Rec. **87**:332, 1915. (*l*) Goodman, C., in discussion on Putnam. (*m*) Buerger, L., in discussion on Putnam. (*n*) Tilton, B. J., in discussion on Putnam. (*o*) Bissell, J. B.: The Field of Surgery in Arteriosclerosis, New York M. J. **101**:993-995, 1915. (*p*) Meyer, W.: Final Result of Arteriovenous Anastomosis (Femoral) for Gangrene of Foot, Ann. Surg. **62**:630, 1915.

2. (*a*) Gallois, and Pinatelle: Un cas d'anastomose artério-veineuse longitudinale pour artérite obliterante, Rev. chir. **23**:236-250, 1903. (*b*) Coenen, H., and Wienwiorowski: Über das Problem der Umkehr des Blutströmes und die Wieting'sche Operation, Beitr. klin. Chir. **75**:313-367, 1911. (*c*) Stetten, D.: The Futility of Arteriovenous Anastomosis in the Treatment of Impending Gangrene of the Lower Extremity, Surg., Gynec. & Obst. **20**:381-402, 1915.

(Footnote continued on next page)

of therapeutic femoral arteriovenous shunt gradually lost its popularity, and between that year and the year 1948 it is rarely cited in the literature.[3] Indeed, it had been virtually forgotten as a practical surgical procedure when in 1949 it was revived by Jordan and Johnston [4] in this country and by Leger [5] in France.

In the past the clinical and experimental experiences with the operation yielded inconsistent and often conflicting results. Most of the experimental investigators found that a significant degree of diversion of the arterial blood into the veins of the lower extremity was not possible, mainly because of the presence of venous valves.[6] On grounds of general physiological considerations also, the possibility of a reversal of the circulation of the lower limb would seem slight. There are, on the other hand, a considerable number of clinical reports, some of recent date, of striking therapeutic successes attributed to the operation.[7] However, the question of whether these successes were fortuitous or whether they were in fact brought about by the diversion of the arterial blood cannot be answered, since objective methods of investigation were almost never applied in the postoperative study of the circulatory effects of the arteriovenous shunt. Yet the question is of obvious importance; the value of

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(*d*) Horsley, J. S., and Whitehead, R. H.: A Study of Reversal of the Circulation in the Lower Extremity, J. A. M. A. **64**:873-877 (March 13) 1915. (*e*) Horsley, J. S.: The Uses and Limitations of Blood Vessel Suturing, with Special Reference to Reversal of the Circulation, South. M. J. **8**:962-966, 1915; (*f*) Reversal of the Circulation in the Lower Extremity, Ann. Surg. **63**:277-279, 1916; (*g*) Operative Treatment of Threatened Gangrene of the Foot, with Special Reference to Reversal of the Circulation, J. A. M. A. **67**:492-499 (Aug. 12) 1916.

3. (*a*) Roussiel, M.: L'anastomose artérioveineuse dans le traitement des gangrènes par obliteration arterielle, J. Chir. **16**:257-277, 1920. (*b*) Radlinski, quoted by Antonucci, C.: Un nuovo schema di anastamosi arterio-venosa nella cura delle gangrene degli arti inferiori da endoangioite obliterante, Arch. ed atti Soc. ital. chir. **36**:756-762, 1930. (*c*) Diaz Sarasola, R.: Un caso de operación de San Mártin, Arch. cardiol. y hemat. **10**:137-143, 1929. (*d*) Antonucci, C.: Un nuovo schema di anastomosi artero-venosa nella cura delle gangrene degli arti inferiori da endoangioite obliterante, Arch. ed atti Soc. ital. chir. **36**:756-762, 1930. (*e*) Zanardi, F.: Sul valore chirurgico e fisiologico dell'anastomosi artero-venosa, Arch. ital. chir. **26**:463-484, 1930. (*f*) Trincas, M.: La anastomosi arterio-venosa nel morbi de Raynaud, Reforma med. **47**:203-209, 1931. (*g*) Bernheim, B. M.: Arteriovenous Anastomosis: Follow-Up After 18 Years of Successful Reversal of the Circulation in all Four Extremities of the Same Individual, J. A. M. A. **96**:1296-1297 (April 18) 1931. (*h*) Vitale, A.: L'anastomosi arterio-venosa (contributo sperimentale), Arch. ed atti Soc. ital. chir. **38**:864-887, 1932. (*i*) Voss, O.: Beitrag zur arterio-venösen Anastomose, Beitr. klin. Chir. **159**:414-423, 1934. (*j*) Lozzi, V.: L'anastomosi artero-venosa nella chirurgia dei grossi vasi, Rinasc. med. **12**:53-55, 1935. (*k*) Gioja, E.: Sulla possibilità di inversione del circolo sanguigno con particolare riguardo al rene: (Ricerche sperimentali), Bull. Soc. med.-chir., Pavia **49**:345-387, 1935.

4. Jordan, P.: Arteriovenous Shunts for Revascularization of Ischemic Limbs, J. Michigan M. Soc. **48**:1011-1012, 1949. Jordan, P., and Johnston, C. G.: The Use of Arterio-Venous Shunts in Ischemic Limbs, in Proceedings of the Thirteenth Congress of the International Society of Surgery, New Orleans, Oct. 10-16, 1949, p. 933.

5. Leger, L.: Essai de revascularisation d'un membre par anastomose artério-veineuse termino-terminale, Presse méd. **57**:1198-1200, 1949.

6. Coenen and Wienwiorowski.[2b] Stetten.[2c] Horsley.[2f] Zanardi.[3e] Trincas.[3f] Vitale.[3h] Gioja.[3k]

7. Wieting.[1e] Bernheim.[1f] Goodman.[1g] Lilienthal.[1i] Putnam.[1k] Meyer.[1p] Radlinski.[3b] Diaz Sarasola.[3c]

any operative procedure that offers hope of improvement in the treatment of occlusive arterial disease deserves careful appraisal. It seemed worth while, therefore, to re-evaluate the operation of therapeutic femoral arteriovenous anastomosis by means of instrumental as well as clinical criteria.

MATERIAL AND METHODS

Selection of Cases.—Since on the basis of both the recorded clinical experience and the physiological principles the operation seemed to carry definite risks, only

TABLE 1.—*Summary of Clinical Data*

Case	Sex	Age	Type and Degree of Vascular Disease	Type and Level of Anastomosis	Evidence and Duration of Patency of Shunt	Effects of Shunt			Level of Amputation
						Discoloring of Foot and Leg	Swelling of Foot	Ischemic Changes	
1	M	60	Arteriosclerosis (diabetes); early gangrene of toes of left foot	Side-to-side; superficial femoral	Exploration, 8 days; arteriogram, 8.5 mo.	Present	Present	Worse	I. Transtibial guillotine II. Supracondylar
2	F	66	Arteriosclerosis (diabetes); ischemic ulcer 3 by 5 cm., left medial malleolus	Side-to-side; superficial femoral	Exploration, 9 days	Present	Present	Worse	Transtibial guillotine
3	M	66	Arteriosclerosis; ischemic ulcer 3 by 5 cm., left heel	Side-to-side; common femoral	Arteriogram, 9 mo.	Present	Present	Worse	Supracondylar with 1 revision
4	M	63	Arteriosclerosis; gangrene of left 1st toe	Side-to-side; superficial femoral	Exploration, 11 days	Present	Present	Worse	I. Transtibial plastic II. Supracondylar with 1 revision
5	M	68	Arteriosclerosis; early gangrene of toes and dorsum of right foot	End-to-end; superficial femoral	Arteriogram, 5.5 mo.	Present	Present	Worse	Supracondylar
6	M	59	Arteriosclerosis (diabetes); gangrene of right 1st toe	End-to-end; superficial femoral	Exploration on 9th postoperative day; closed	Present	Present	Worse	I. Transtibial guillotine II. Supracondylar
7	M	31	Thromboangiitis obliterans; impending gangrene, right foot	End-to-end; superficial femoral	Exploration on 19th postoperative day; clinically closed on 4th-6th postoperative day	Present	Present	Worse	I. Transtibial guillotine II. Supracondylar
8	M	74	Arteriosclerosis; ischemic ulcer 3 by 2 cm., right foot	End-to-end; superficial femoral	Clinically closed on 8th postoperative day	Present	Present	Worse	I. Supracondylar II. Midthigh with 1 revision
9	M	58	Arteriosclerosis (diabetes); gangrene of right 1st and 2d toes	End-to-end; superficial femoral	Arteriogram, 7 wk.	Slight	None	Worse	I. Transtibial guillotine II. Supracondylar with 2 revisions

patients that had failed to respond to less aggressive methods of treatment were selected for study. All patients under consideration either had had long and unsuccessful trials with various vasodilator drugs and/or lumbar sympathectomy or had manifested a more or less rapid progress in the ischemic changes. Eight cases of arteriosclerosis and one case of thromboangiitis obliterans were studied. The pertinent clinical data in these cases are listed in Table 1. As can be seen, all patients but one had definitely established gangrene which, however, was of the dry, noninfected type and was limited to the foot (usually to the toes). Thus, the aim of the operation was to prevent the spread of gangrene and to reduce to the minimum the extent of amputation that seemed unavoidable.

Selection of Operative Procedure.—The conventional surgical approach to the common femoral artery, with its limited amount of dissection, in the performance of femoral arteriovenous anastomosis was found unsatisfactory since it failed to supply the necessary anatomic information for a rational choice of operative technic. It is the minimal requirement for a therapeutic femoral arteriovenous shunt that it must not interfere with the arterial blood supply of the thigh and that it must leave an adequate venous network for the drainage of the limb. The anastomotic site that will ascertain the fulfillment of this requirement cannot be determined unless the relationship of the bifurcation of the common femoral artery to the common femoral vein and its main tributaries is clearly demonstrated. The disposition of the valves of the superficial femoral vein as well as the functional state of the superficial femoral artery must also be known before a judgment can be reached regarding the optimal site and functional usefulness of the anastomosis. Since the pattern of the femoral venous [8] and, to a less extent, arterial [9] system is variable, since the number and arrangement of the venous valves are unpredictable, and since the arteriosclerotic changes in the femoral arteries vary from segment to segment, the entire femoral triangle and the proximal half of the adductor canal must be dissected out in order to obtain the required anatomic orientation. Such a dissection, with identification of all the major vessels, was performed in all but the first two cases, in which the adductor canal was not entered.

In the first four cases, for reasons of greater safety, the arteriovenous communication was made between the superficial femoral vessels,[10] in a side-to-side manner with ligation of the proximal limb of the vein. Since later experience showed that in cases selected on the basis of the criteria mentioned above the anastomosis could be made with end-to-end technic without increasing the danger of the loss of limb, in Cases 4 to 9 end-to-end anastomoses were done. With the exception of Case 3, in which the anatomical features permitted a common femoral anastomosis, the level was distal to the origin and point of emptying, respectively, of the deep femoral artery and vein.

Methods of Investigation.—The measure of the clinical success of the operation was considered to be the degree to which it fulfilled its aim, which was the prevention of the progress of gangrene and the reduction of the extent of amputation if this became necessary. Subjective observations on the affected limb postoperatively, noting the progress of the ischemic changes as well as other alterations in the appearance of the limb, were recorded. Investigations were also carried out to ascertain whether arterial blood had been effectively diverted into the venous channels to measure the mode and extent of this diversion, if present.

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8. Edwards, E. A., and Robuck, J. D., Jr.: Applied Anatomy of the Femoral Vein and Its Tributaries, Surg., Gynec. & Obst. **85**:547-557, 1947.

9. Senior, H. D.: Description of Larger Direct or Indirect Muscular Branches of Human Femoral Artery: Morphogenetic Study, Am. J. Anat. **33**:243-265, 1924. Williams, G. D.; Sindelar, R. J., and McIntire, L. R.: Origin of the Deep and Circumflex Femoral Group of Arteries, Anat. Rec. **60**:189-196, 1934.

10. In the English and B. N. A. anatomic nomenclature the adjective "superficial" is not applied to the femoral vessels. From the surgeon's practical point of view, however, this designation is very useful. In this discussion, that part of the femoral artery and vein distal to the point of origin of the deep femoral artery and to the point of emptying of the deep femoral vein, respectively, is called superficial femoral artery and vein.

In the determination of the rate of flow or volume flow of the blood in the affected limb the histamine-fluorescein wheal test,[11] while subject to limitations, proved to be a workable method. The test was performed essentially as described by others.[11a,b] Use was also made of skin temperature determinations, the readings having been taken with electric thermocouples at stated intervals along the limb. Since the ambient temperature was not standardized, the results were expressed by comparing the temperature readings of the affected side with those of the unaffected side.

Since the volume flow of blood (or rate of blood flow) is, among other factors, dependent on the pressure differences between two given points in the vessel,[12] the measurement of these pressure differences, the other factors being constant, is a good index of the volume flow. In Cases 5 to 9 the moment-to-moment changes of blood pressure at various levels in the components of the arteriovenous shunt were measured with an electronic manometric system for recording biologic pressure variables formerly described by others.[13] The changes in pressure were observed on a monitoring oscilloscope, and tracings were made on a photographic recording oscillograph both before and after the creation of the shunt. The measurements were repeated after one or more valves were appropriately cut following a temporary shunt over a vitallium tube. Special pressure readings by means of venous retrograde catheterization were taken in Case 9.

The path of the arterial blood was followed by means of arteriography. The arteriograms were obtained mostly by open single-exposure technique at the time of the performance of the shunt and at the subsequent exploration of the incision. In the later phase of the study equipment was available for multiple-exposure closed angiography. In a few cases preoperative and postoperative phlebograms were also taken.[14]

The venous pressure at the midleg and the changes in the circumference of the extremity were measured at intervals preoperatively and postoperatively.

FINDINGS

The Duration of the Patency of the Anastomosis.—The exact determination of the length of time during which the anastomosis stays open after the creation of an arteriovenous shunt is of obvious importance in judging its effectiveness. In the past the methods used to determine this interval were practically always indirect and unreliable. In only one case on record was a postoperative arteriogram taken to demonstrate the path of the blood flow distal to the shunt.[6] In the present study, the state of the anastomosis in Cases 1, 2, 4, 5, and 7 was ascertained by reopening the shunt, inspecting the operative field and taking arteriograms under direct vision.

11. (*a*) Netter, J. L., and Schmidt, E. R.: Wheal-Fluorescence: New Method of Evaluating Peripheral Vascular Diseases: Preliminary Report, Ann. Surg. **121**:328-337, 1945. (*b*) Netter, J. L.: The Use of Fluorescent Wheals in Determining Extent and Degree of Peripheral Vascular Insufficiency: Further Observations, ibid. **122**:898, 1945. (*c*) Sicher, W. D.: Circulation Time of Extremities Using Intravenous Administration of Fluorescein: Preliminary Report, Proc. Staff Meet., Mayo Clin. **18**:515-521, 1943. (*d*) Massell, T. B.: Fluorescein Wheal Test for Collateral Circulation in Preoperative Evaluation of Patients with Aneurysms and Arteriovenous Fistulas, Surgery **21**:636-645, 1947. (*e*) Kramer, D. W., and Abramson, E. B.: Fluorescein Studies in Peripheral Vascular Disorders, Am. J. M. Sc. **214**:368-371, 1947. (*f*) Mentha, C.: Essai d'application du test histaminique à l'étude des affections vasculaires des membres, Arch. mal. coeur. **41**:25-33, 1948.

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In Cases 3, 6, and 9 the condition of the shunt was investigated by multiple-exposure closed arteriograms. In Case 8 the clinical course (thrombosis of the common femoral artery with gangrene extending to the midthigh) left no doubt about the failure of the anastomosis, and no special investigation was done. For practical reasons, it seemed most suitable to do the exploration eight to nine days after the performance of the anastomosis. Occasionally the interval had to be longer. The results of these investigations are given in Table 1. In brief, six of the anastomoses remained open from eight days to five and a half months postoperatively; four of these shunts appeared to be still functioning at the time of the last clinical examination, up to 12 months postoperatively. It may be added that the condition of the arterialized femoral vein could be checked by direct inspection whenever a supracondylar amputation was performed (in all but Case 2); such an inspection confirmed the findings gathered by other means in every instance. As regards the factors that led to the occlusion of the site of anastomosis, technical errors probably did not play an important role.

In an evaluation of the clinical effectiveness of the operation, the cases that did not reveal a patent shunt at least eight days after the performance of the anastomosis obviously must be excluded. In a study of the physiological effects of the operation, however, the findings gathered in these cases have a definite comparative value.

Clinical Effects of the Shunt.—The changes in the limb after arteriovenous anastomosis that could be determined without instrumental means were uniform. There was a change of varying intensity in skin color to a dusky red, extending over the lower half or two-thirds of the leg. The onset of this change was often practically immediate. Some engorgement of the superficial veins could almost invariably be noted, and pretibial edema developed in all but Cases 7, 8 and 9. Visible pulsation of the superficial veins was never observed. The patient usually complained of some annoying fulness in the leg, but serious or unbearable discomfort never appeared. Tenderness of the calf was frequent. If there had been pain before, it was not appreciably influenced by the operation. All these changes were similar to those commonly seen in thrombosis or other obstruction of the femoral venous system. Without exception the ischemic changes in the foot showed persistent progression the pace of which was usually somewhat more rapid than before the operation. In Case 5 a previously dry gangrene became moist. There were no systemic changes that could be ascribed with certainty to the effect of the newly created arteriovenous communication.

As shown in Table 1, every patient had to undergo amputation. In order to derive every possible benefit, no matter how remote, from the arteriovenous shunt, a deliberate attempt was made to do a low amputation even if the objective signs did not warrant it. Thus, in Cases 1, 2, 4, 5, 7, and 9 an amputation through the middle or upper third of the leg was first carried out, but only in Case 2 was primary healing obtained, the remainder eventually requiring supracondylar amputation. In Case 3 a primary supracondylar level was chosen since the shunt had been done between the common femoral vessels. In Case 6 the patient insisted on the higher level. In Case 8 thrombosis of the site of anastomosis and of the deep femoral artery made a midthigh amputation imperative. There was a high incidence of healing complications in the supracondylar amputations. Only four of the eight healed per primam, while in Cases 3, 4, 8, and 9 one or more revisions were necessary. Whether one

considers the series as a whole or only the cases with functioning anastomosis, it is evident that the end results are not superior to those obtained in similar cases without the use of arteriovenous anastomosis, since in the presence of the degree of circulatory impairment which these cases showed good healing can be almost always obtained with any of the various routine supracondylar procedures and often even with a transtibial amputation. In view of the poor healing in the primary and secondary supracondylar amputations of the series, one must even regard the ultimate results as inferior to the average. (The poor healing, however, must not be ascribed solely to the physiological effects of the arteriovenous shunt. The deliberate attempt to obtain an amputation level below the knee, the extensive operative incision in the thigh, and the unavoidable additional trauma of the reexamination of the thigh wound may also have contributed to the development of wound complications.) In terms of the primary clinical aim of arteriovenous anastomosis, that is, the salvage of some length of the limb, the procedure was in this series uniformly unsuccessful.

Effects of the Shunt on the Rate and Direction of Blood Flow.—The validity of conclusions drawn from the clinical results just described is limited by two factors. First, the series studied was small, with a large element of chance inherent in small samples. Secondly, the cases were advanced, and therefore the objection can be raised that even successful diversion of the blood into the venous vascular bed might not have influenced their course. The findings gathered with objective means of investigation on the rate and direction of the blood flow in the affected limbs, besides throwing light on the fundamental physiologic effects of the shunt, are thus significant also from the point of view of the clinical evaluation of therapeutic femoral arteriovenous anastomosis.

Effects on the Rate of Blood Flow: It is correct to assume that a successful diversion of the blood from the reduced arterial bed of the diseased limb into an ample and open venous vascular tree would result in an increased rate of arterial blood flow to the extremity.

The results obtained with skin temperature determinations as an index of the rate of blood flow (Table 2) were variable but showed a general trend of elevated readings postoperatively. Among the five cases in which a sufficiently large number of observations was recorded this trend was noticeable in all but one (Case 8). The other indirect method of determination of blood flow that we used, the histamine-fluorescein wheal test (Table 3), disclosed slight improvement in three cases (Cases 2, 4 and 7) and deterioration in two (Cases 5 and 6); in 3 cases no change was noted, and in one case (Case 8) postoperative arterial thrombosis rendered the result meaningless. In the interpretation of the results of both of these indirect methods, aside from their well-known and considerable inherent limitations, several factors particular to the conditions of their application in these cases must be borne in mind. Elevation of the general body temperature, local hyperemia in the area of operation and the tissue changes near the area of gangrene were such factors. (As regards the last-named factor, in Cases 6 and 7 the most marked postoperative increase in skin temperature was recorded near the gangrenous portion of the limb.) Moreover, the tests indicated an improved blood flow almost as frequently in cases with nonfunctioning shunts as in those with open anastomoses. Thus the occasional slight increase in the rate of blood flow indicated by these tests, if at all significant, cannot be regarded as the result of a diversion of the arterial blood stream.

TABLE 2.—*Comparison of Preoperative and Postoperative Skin Temperatures* *

Case	Level	Preoperative	Postoperative Day		
			1 to 3	4 to 7	8 to 24
1	Thigh	.....	.....	.....	.....
	Upper leg	.....	.....	.....	.....
	Midleg	−3.5	+3.8	.....	.....
	Lower leg	−6.8	+1.3	.....	.....
	Foot	−8.3	+1.6	.....	.....
5	Thigh	.....	+1.7	+3.8	+3.0
	Upper leg	.....	+4.0	+3.6	+4.4
	Midleg	.....	+6.0	+4.2	+3.8
	Lower leg	.....	−0.6	+2.6	+2.9
	Foot	.....	.....	−3.2	−2.8
6	Thigh	+3.0	−2.4	−3.8	−0.8
	Upper leg	+1.5	−2.4	+0.1	+0.9
	Midleg	+1.6	−2.3	0.0	−6.2
	Lower leg	−0.8	+2.4	+2.4	+2.6
	Foot	−1.3	+3.9	+0.3	+8.3
7	Thigh	−0.3	−2.7	−0.1	+1.4
	Upper leg	−2.2	+0.3	+4.5	+2.6
	Midleg	−5.0	+2.0	+5.8	+6.0
	Lower leg	−9.6	−4.1	+3.2	−3.1
	Foot	−14.8	+5.8	+7.0	+6.2
8	Thigh	−0.5	−2.5	−4.5	−3.8
	Upper leg	0.0	−1.5	+4.5	−4.1
	Midleg	−1.5	+1.5	−4.1	−4.5
	Lower leg	−5.0	−3.1	−6.3	−6.1
	Foot	−5.5	−5.5	−9.6	−5.5
9	Thigh	+1.0	−7.0	−0.5	−0.6
	Upper leg	−1.2	−1.8	+1.5	+3.8
	Midleg	+4.3	−4.3	−2.4	−3.6
	Lower leg	+1.9	−1.4	−0.3	−3.6
	Foot	+0.9	−3.4	+0.4	−0.6

* All figures represent the arithmetic differences between the temperature readings of the lower limbs (in F.). The preoperative values as well as the postoperative values in Case 5 were obtained by subtracting the readings at corresponding levels in the affected limb from those for the unaffected limb. In order to arrive at the postoperative values in all but Case 5, the postoperative skin temperature differences between the limbs were also calculated; by subtracting from these values the preoperative differences, the figures listed were obtained. Thus plus values mean a higher temperature at a given time and level in the affected limb and minus values a lower temperature in the affected limb.

TABLE 3.—*Results of Preoperative and Postoperative Histamine-Fluorescein Wheal Tests* *

Case	Level	Preoperative	Postoperative Day		Case	Level	Preoperative	Postoperative Day	
			4 to 7	8 to 24				4 to 7	8 to 24
1	Thigh	2+	2+	...	5	Thigh	4+	...	4+
	Upper leg	1+	1+	...		Upper leg	3+	...	3+
	Midleg	0	0	...		Midleg	3+	...	0
	Lower leg	0	0	...		Lower leg	2+	...	0
	Foot	0	0	...		Foot	0	...	0
2	Thigh	3+	...	3+	6	Thigh	4+	3+	3+
	Upper leg	1+	...	2+		Upper leg	3+	1+	1+
	Midleg	0	...	1+		Midleg	3+	0	0
	Lower leg	0	...	0		Lower leg	3+	0	0
	Foot	0	...	0		Foot	2+	0	0
3	Thigh	3+	3+	...	7	Thigh	4+	...	4+
	Upper leg	1+	1+	...		Upper leg	1+	...	3+
	Midleg	0	0	...		Midleg	0	...	0
	Lower leg	0	0	...		Lower leg	0	...	0
	Foot	0	0	...		Foot	0	...	0
4	Thigh	4+	3+	3+	8	Thigh	4+	...	0
	Upper leg	1+	2+	2+		Upper leg	0	...	0
	Midleg	0	2+	2+		Midleg	0	...	0
	Lower leg	0	0	0		Lower leg	0	...	0
	Foot	0	0	0		Foot	0	...	0
					9	Thigh	4+	3+	4+
						Upper leg	2+	2+	2+
						Midleg	0	0	0
						Lower leg	0	0	0
						Foot	0	0	0

* The standards of grading (1+ to 4+) were based on the intensity and rapidity of appearance of the fluorescence in the wheal. The scale was as follows: 4+ indicated marked fluorescence in less than one minute; 3+, marked fluorescence in more than one minute but less than two minutes; 2+, moderate fluorescence in less than four minutes, and 1+, moderate fluorescence in more than four but less than five minutes.

As formerly mentioned, the rate of blood flow can be evaluated in terms of the pressure differences between two given points in the vessel, other factors being assumed to be constant. The results obtained by measuring the moment-to-moment blood pressure changes in the various intervalvular segments of the venous component of the shunt were instructive. Figure 1 consists of reproductions of pressure curves obtained with the method formerly described. Figure 2 is a pictorial summary of the findings.

The manometric observations, obtained with great consistency in all the five cases so studied, not only demonstrated a marked drop in the blood pressure and thus—under the existing conditions—in the rate of blood flow in the venous component of the anastomosis but also showed that the decrease occurred at points

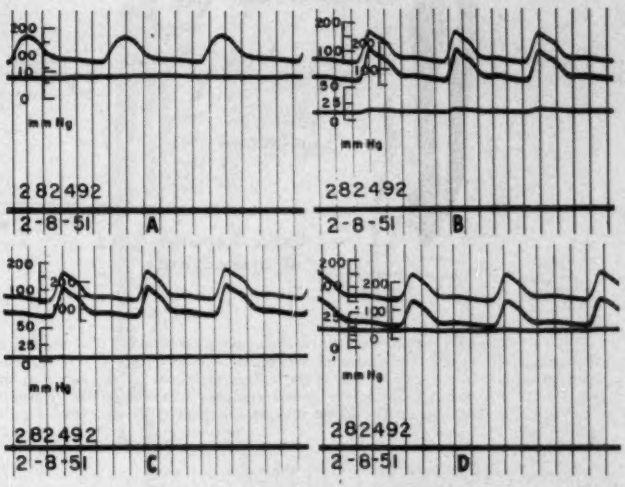

Fig. 1.—Blood pressure tracings in Case 9.

A, blood pressure curves from the superficial femoral artery (upper) and superficial femoral vein (lower) before establishment of the shunt. (Vertical lines denote time intervals of 0.1 sec.)

B, blood pressure curves, after temporary anastomosis, from the superficial femoral artery (upper), superficial femoral vein directly distal to the shunt (middle), in from a segment of the arterialized superficial femoral vein separated from the shunt by one valve (lower). Because of the change in the vascular bed resulting from the anastomosis, the contour of the arterial pressure wave is altered. The contour of the arterial pulse persists in the pressure tracing from the segment of the vein directly distal to the anastomosis and proximal to the first valve. The lower curve, taken from a point separated from the shunt by one valve, is the record of the pressure relations below a relatively competent valve through which a slight leak occurs causing a minimal pulse ripple. The static pressure is slightly elevated.

C, blood pressure curves after temporary anastomosis. The upper and middle curves were obtained with the needles in the same position as in *B*. The lower curve is a tracing of the pressure recorded through a needle distal to two valves; the contour of the pressure wave is flat, only a static pressure being recorded.

D, blood pressure curves after sectioning all venous valves but the distalmost one (not reached by the valvulotome) and after the completion of the permanent anastomosis. The upper and middle curves were recorded as in *B* and *C*; the lower curve was traced with the needle just distal to the remaining (uncut) valve. The pulse wave has disappeared, and the static pressure is about the same as in *B*, also distal to one valve.

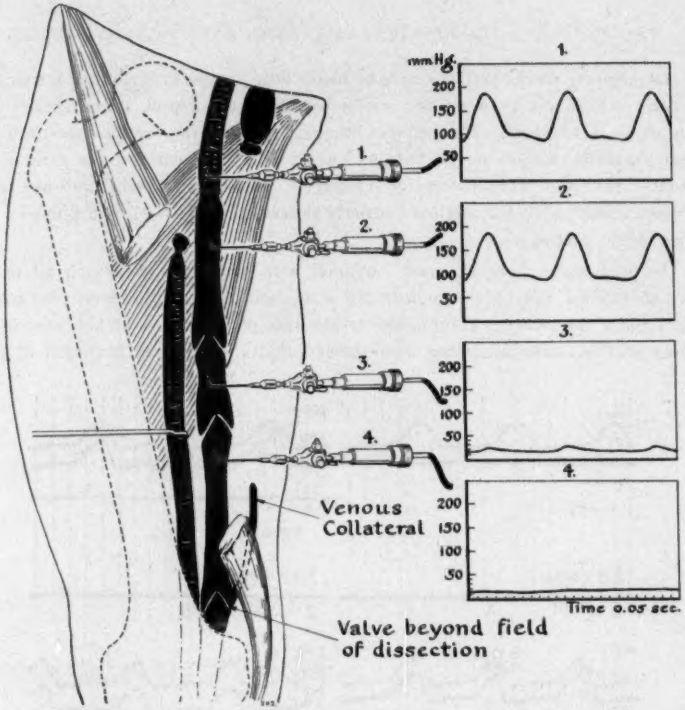

Fig. 2.—Pictorial summary of the results of manometric studies. The cumulative decrease of blood pressure caused by the resistance of succeeding valves in Case 9 is shown diagrammatically but approximately on scale. Even if the valves proximal to the points of insertion of needles 3 and 4 were cut, inaccessible valves would continue to dissipate the transmitted blood pressure and eventually short-circuit the blood into an adjacent collateral vein.

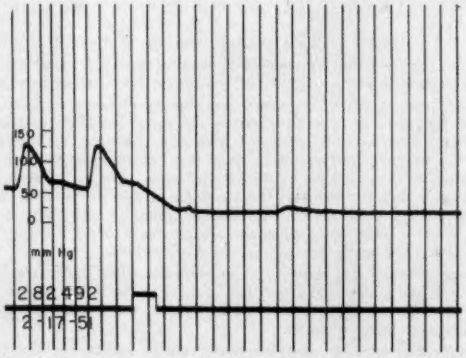

Fig. 3.—Blood pressure curve from the arterialized superficial femoral vein obtained, 10 days after the establishment of arteriovenous shunt, during the withdrawal of a catheter formerly introduced during transtibial amputation through the popliteal vein to the level of the shunt (Case 9). The mark on the base line denotes the moment, determined by radiographic control, when the tip of the catheter passed the most proximal competent valve. First a pulsatile pressure is observed, but as the catheter is withdrawn the pulsations suddenly stop when the catheter passes the highest intact valve, and thereafter only an elevated static venous pressure is recorded. Thus in 10 days the competence of the valve had not been compromised.

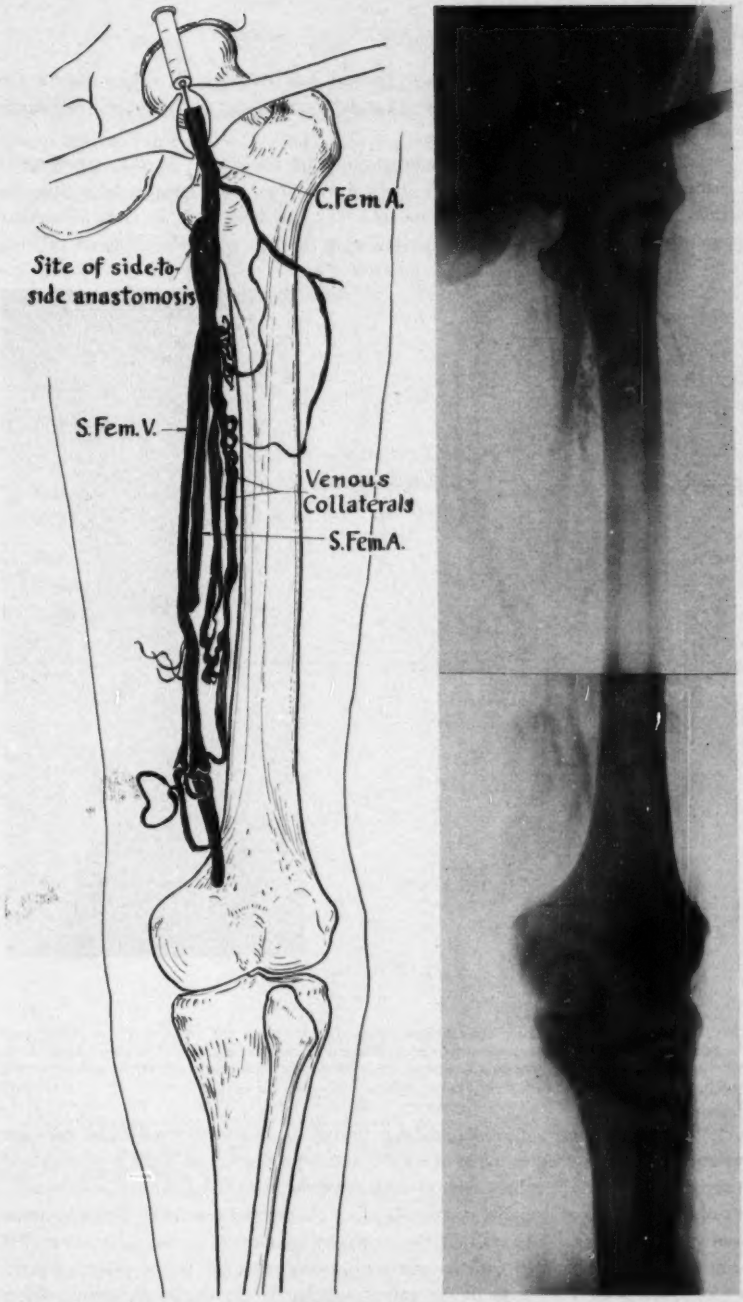

Fig. 4.—Open single-exposure arteriogram taken on the eighth day after side-to-side superficial femoral arteriovenous anastomosis (Case 1). The superficial femoral vein shows filling to the level of the upper popliteal region. Numerous venous collaterals carry the dye centripetally. The superficial femoral artery is only partially patent.

distal to valves. The experiments also proved that although all valves impede the flow of blood to some extent they are not equally competent and that their resistance is cumulative.

From these findings certain assumptions can be made. In the experiments described, the segment of the vein studied was free from collaterals within the operative field, or if collaterals had existed they had been tied; in such a vascular channel the force of the transmitted pulse, being confined and directed in its entirety

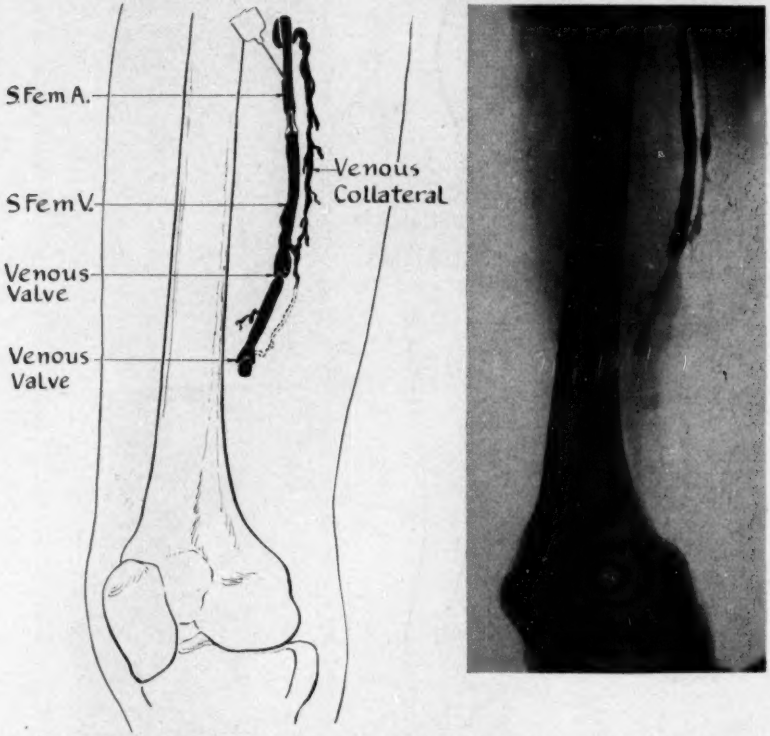

Fig. 5.—Open single-exposure arteriogram taken directly after the creation of an end-to-end superficial femoral arteriovenous shunt over a Blakemore tube (Case 7). The dye passes to a point slightly distal to the midthigh, where it is evidently stopped by a valve and returned through a true anatomical collateral vein.

against the obstructing valves, could be expected to overcome readily the valvular resistance. Pressure studies made in Case 9 and reproduced in Figure 3 proved that the resistance of certain valves even in such circumstances is lasting. Under conditions of undisturbed anatomical relationships, of course, the arterialized vein is not a closed vascular channel. As abundantly shown by anatomical studies, the valves are almost invariably associated with tributaries opening proximal to the valve. Under these conditions the resistance of the valves will tend to force the blood into these

collaterals whenever the valvular resistance is greater than the intraluminal resistance of the associated collateral. If this is true, the distal progression of the diverted blood stream will come to an end when the volume of blood which can be delivered by the anastomosis is equal to the sum of the volumes carried away by the venous collaterals, the lowermost collateral being the one in which the pressure is less than

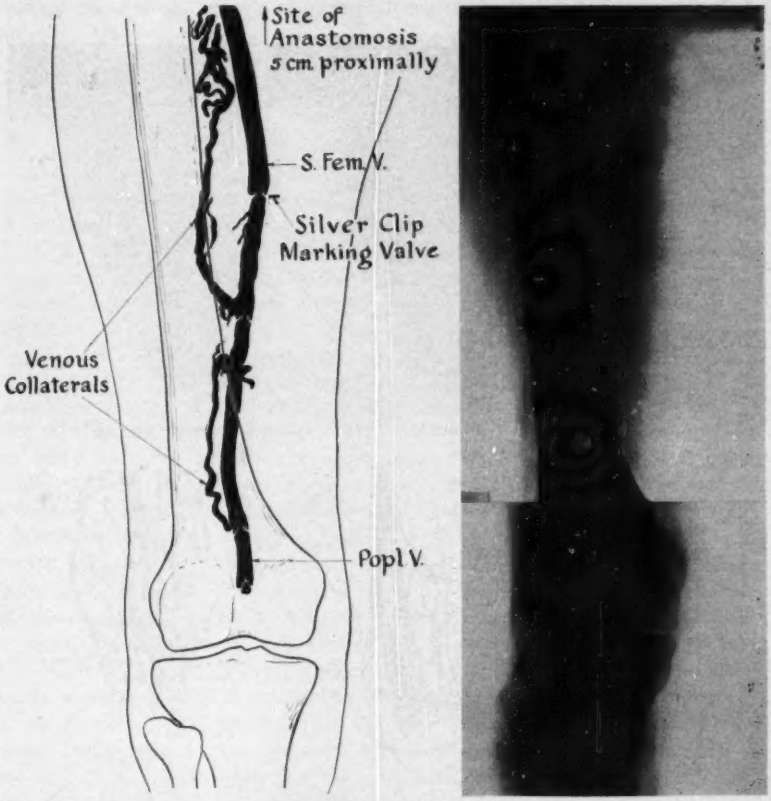

Fig. 6.—Closed (composite) arteriogram selected from a series of eight exposures, taken on the ninth day after end-to-end superficial femoral arteriovenous anastomosis (Case 9). The dye advances to the upper popliteal region after passing through three valves each of which is only partially competent but the distal two of which exert enough resistance to divert part of the dye into adjacent collaterals. The valve marked with a silver clip (also mentioned in the legend for Figure 3) was the distalmost competent one noted during operation; it lacks an adjacent tributary, but its role in reducing the transmitted arterial blood pressure was clearly demonstrated. (See text and Figure 3.)

that needed in the arterialized femoral vein to force to any degree the adjacent valve. The correctness of these assumptions can be readily tested by arteriography.

The Direction of Blood Flow After the Shunt: Open arteriograms were taken in Cases 1, 2, 4, 6, 7, and 8 immediately before and after the creation of the shunt.

In Cases 1, 2, 4, and 6 the arteriogram was repeated at the time of the reopening of the operative incision 8 to 19 days postoperatively. At intervals of one and a half to eight and a half months postoperatively follow-up arteriograms were taken in Cases 1, 3, 5, and 9.

The findings gathered from the arteriograms were remarkably consistent. There was no instance in which the contrast medium was observed to pass beyond the popliteal space; often it stopped at short distances (4 to 10 cm.) distal to the anasto-

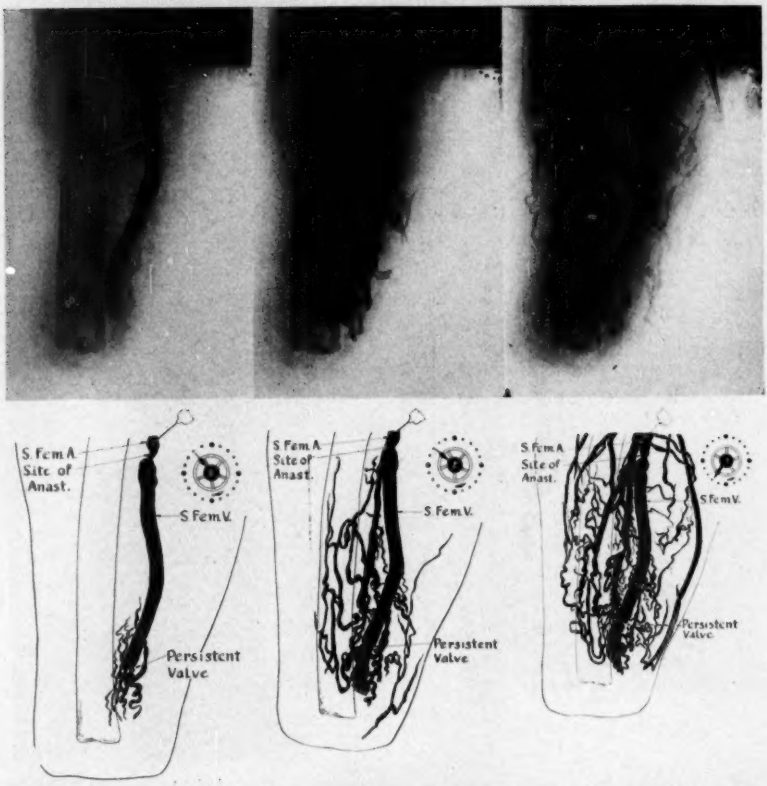

Fig. 7.—Closed multiple-exposure arteriograms taken five and a half months after the creation of an end-to-end superficial femoral arteriovenous shunt (Case 5). A striking expansion of the venous collateral bed is noted. A valve near the distal end of the arterialized superficial femoral vein is still partially competent. (Note hesitation in the passage of dye.)

mosis (Cases 2, 4, and 6), but more often it reached the midportion of the adductor canal, 25 to 30 cm. distal to the anastomosis (Cases 1, 3, 5, 7, 8, and 9; Figs. 4 to 7). The point of arrest appeared always to correspond to a valve. The further path of the dye at times was not clear partly because of the difficulty of correct timing in single-exposure arteriography and partly because of the small size of the collateral veins immediately after the establishment of the shunt. The return path was clearly

indicated, however, in Cases 1, 2, 7, and 9 even in the roentgenograms taken directly after the creation of the shunt (Figs. 4, 5, and 6), and it was invariably a tributary associated with the valve whose resistance had brought to an end the forward passage of the contrast medium. In roentgenograms obtained in cases with functioning shunts several days to several months after the original operation the collateral branches appeared progressively clearer, larger and more complex (Cases 1, 3, 5, and 9). The collateral venous bed may eventually undergo a striking expansion (Fig. 7). The follow-up angiograms also reveal that the obstructing valve remains a barrier for long periods of time. In Cases 5 (Fig. 7) and 9 valves were seen to be almost completely competent five and a half months and seven weeks, respectively, after the establishment of the shunt.

COMMENT

The angiographic evidence fully supports the assumptions made earlier with respect to the role of the venous valves in reducing the rate of blood flow in the arterialized vein and in diverting the blood stream into collateral venous tributaries. From the results of the manometric and roentgenographic studies, the sequence of events may be reconstructed as follows: The shunted arterial blood stream encounters resistance at each valve within the lumen of the arterialized vein. Although the leaflets of the valves in the dilated venous segment do not close in complete apposition, each offers enough resistance to reduce the pulse pressure distal to the valve, with a consequent decrease in the rate of flow. Whenever a valve is reached whose associated tributary vein offers less resistance than the valve, the blood is shunted into the tributary. Before it arrives at the midpopliteal region all the arterial blood stream, or nearly all, has been thus short-circuited centripetally. There is no opportunity for the blood pressure to break down all the successive tiers of valvular structures, since the blood stream has been diverted from the main venous trunk after the forcing of one to three valves.

The short-circuiting of the arterial blood into the venous collaterals distal to the anastomosis must reduce the venous vascular bed available for drainage of the limb already somewhat impaired by the establishment of the arteriovenous shunt, which, from this point of view, is equivalent to a ligation of the superficial femoral vein. One would therefore expect the development of some degree of venous congestion in the extremity. In fact, the postoperative appearances of the limbs already described as well as the measurements of the circumference of the limbs and to a lesser extent the superficial venous pressure determinations [15] indicate that obstruction of the venous return often does take place. Anatomic variations in the available collaterals must significantly influence the degree of this venous obstruction, but in general it was observed to be more marked when the shunt was functioning (Cases 1, 2, 3, 5, and 9).

It is evident from these experiments that the modification of the original arteriovenous femoral shunt by location of its level further distalward or by the addition

15. Among the six cases in which frequent measurements of the circumference of the limbs at predetermined levels were taken preoperatively and postoperatively, all but one (Case 7) showed postoperative swelling. All five cases in which the preoperative and postoperative venous pressure of the affected and unaffected limbs at midleg was determined revealed some increase in the postoperative venous tension on the affected side, although at times the increase was too small to be significant.

of valvulotomy and/or ligation of the collateral veins does not offer any realistic hope of improving its results.

There is a theoretical obstacle in the way of accomplishing a true reversal of the circulation of the lower limb that appears insurmountable and, strangely, has received little attention in the past. In order to improve tissue oxygenation, the diverted arterial blood must be propelled through the venous and arterial capillary bed. Even if this were possible, there would seem to be no serviceable return pathway for the blood from the capillaries proximalward, for the diseased arterial tree surely could not be traversed by the blood under the low pressure existing on the postcapillary side of the vascular system.

While all the foregoing facts appear to refute the feasibility of improving the peripheral circulation by an arteriovenous shunt, the question must also be considered whether attempts at such reversal may not have untoward effects on the already impaired circulation of the limb. Our impression from clinical observations is that the stagnant anoxia that the procedure brings about by the obstruction of the venous return must be an insult added to the damage already done by the ischemic anoxia. Another possibility worthy of inquiry is whether or not the numerous and dilated collateral venous channels that are opened up by the increased pressure within the main venous trunks and through which the arterial blood returns from these trunks may not in effect result in the disturbances of cardiovascular dynamics of an arteriovenous fistula. In Cases 1, 3, and 5 (particularly the last one, Fig. 7), although arteriograms show a very large combined surface of communications between the arterial and venous vascular channels, such changes have not been observed.

It is of some interest to speculate on the possible explanation of the successes reported in the past with the application of femoral arteriovenous anastomosis. As Stetten [2e] pointed out many years ago, some of the postoperative results were exaggerated because of poor follow-up. The lack of objective methods of investigation made the interpretation of clinical and operative observations also often erroneous. In this respect, very likely a common source of error in judging results was the fact that many of the cases in which the operation was performed were instances of early occlusive disease and that the operation was done almost always by the side-to-side technique. In such cases the thrombosis of the venous limb of the shunt, with the arterial component remaining patent (which is not an improbable event), would make the operation physiologically equivalent to a superficial femoral ligation. Ligation of the superficial femoral vein is likely without value in the treatment of obliterative arterial disease of the limb,[16] but the occlusion of the superficial femoral vein under such circumstances would lead to relatively slight disturbances of venous drainage, and any fortuitous improvement might then mistakenly be ascribed to the effects of the operation. A decidedly important factor in many false therapeutic inferences seems to have been the stripping of the femoral artery preparatory to the

16. Glasser, S. T., and Lesser, A.: Femoral Vein Ligation for Chronic Occlusive Arterial Disease: Study of 20 Cases, Am. J. Surg. **52**:100-106, 1947. Glasser, S. T.: Ligation of the Femoral Vein for Chronic Occlusive Arterial Disease: Review of 118 Ligations, Arch. Surg. **50**:56-62 (Jan.) 1945. Mulvihill, D. A.; Harvey, S. C., and Doroszka, V.: Simultaneous Ligation of Vein in Ligation of Large Arteries: Experimental Study, Am. J. Surg. **13**:431-452, 1931. Friedland, C. K.; Hunt, J. S., and Wilkins, R. N.: Effect of Changes in Venous Pressure upon Blood Flow in the Limbs, Am. Heart J. **25**:631-647, 1943.

anastomosis resulting essentially in a periarterial neurectomy, an operation that has a definite if ephemeral vasodilator effect in some cases of occlusive vascular disease. (Our occasional finding of a slight increase in the rate of blood flow by the indirect tests mentioned above in cases in which the shunt had become occluded lends some support to this statement.) One may also mention that interruption of the femoral artery alone has by some been claimed to alleviate the symptoms of these diseases.[17] It seems certain, however, that whatever beneficial effects the operation may have been observed to bring about must have taken place incidentally rather than as the result of the planned "reversal of circulation."

SUMMARY AND CONCLUSIONS

In nine instances of occlusive arterial disease of the lower extremity in which end-to-end and side-to-side femoral arteriovenous anastomosis was performed the clinical results were uniformly poor, both in the three cases in which the shunt became occluded in less than eight days and in the six cases in which the shunt remained open indefinitely. All the cases but one required supracondylar amputation.

The purely clinical as well as the objective (sphygmomanometric and arteriographic) methods of investigation showed in all cases that the arterial blood that had been shunted into the femoral venous trunk failed to progress beyond the popliteal region.

The factor preventing the shunted blood from flowing into the leg was the resistance of the venous valves which reduced the blood pressure in the venous component of the shunt and short-circuited the blood into adjacent centripetal collaterals.

Systemic ill effects attributable to the hemodynamic changes brought about by a functioning shunt did not appear during periods of observation of from seven weeks to nine and a half months, but healing processes in the limb were unfavorably affected.

17. Lewis, D., and Reichert, F. L.: The Collateral Circulation in Thromboangiitis Obliterans: Indication for Ligation of Femoral Artery Just Distal to the Profunda, J. A. M. A. **87**:302-304 (July 31) 1926. Leriche, R., and Fontaine, R.: Conditions nécessaires, résultats et technique de l'artériectomie dans les oblitérations artérielles d'après 80 opérations récents, Presse méd. **43**:1953-1956, 1935. Leriche, R.; Fontaine, R., and Dupertuis, S. M.: Arteriectomy: Follow-Up Studies on 78 Operations, Surg., Gynec. & Obst. **64**:149-155, 1937.

OPERATIVE TREATMENT OF PERIPHERAL ANEURYSMS

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THE TREATMENT of peripheral arterial aneurysms dates back to the time of Antyllus, over 1,600 years ago. Since that time, and particularly since the recent great war, there have been many important advances in this field of surgery. Again, within one decade, large scale warfare is in progress and the added danger of blasts and burns from atomic missiles hangs over our heads. It is therefore timely to review the management of peripheral arterial aneurysms due to injury or disease. Such a discussion must include preventive as well as definitive treatment.

PREVENTION

In World War I, Matas [1] reported that 20 to 25% of injuries involved the vascular system but that aneurysms developed in only 1 to 2% of the casualties. This low occurrence rate was due largely to early death from other causes, such as hemorrhage, sepsis, or gangrene. Today, as a result of our improved methods of emergency control of hemorrhage, better control of shock, intensive use of antibiotic substances, and rapid transportation of the injured persons to emergency hospitals, many more persons survive the initial injury and become subjects for therapy. Recent reports [2] from the Surgeon General's office indicate that the mortality rate from all types of injuries in the Korean theater of war is approximately one-half that of World War II. In World War II, DeBakey [3] reported 502 instances of injury to large arteries, 72.5% of which resulted in the loss of an extremity. With present day technics, it should be possible in most circumstances of war to perform an early repair of the injured major artery by resection of the traumatized segment with an end-to-end anastomosis or the interpolation of a segment of vein to restore the continuity of the main arterial channel. In this way more limbs can be saved and the development of aneurysms can be prevented. These methods would necessi-

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From the Department of Surgery of the College of Medicine, University of Cincinnati, and the Lucie Rawson Laboratory for Vascular Research of the Cincinnati General Hospital.

1. Matas, R.: Military Surgery of the Vascular System, in Keen's Surgery, Philadelphia, W. B. Saunders Company, 1921, Vol. 7, pp. 713-819.

2. Robinson, P. I.: Address before the Cincinnati Veterans Physician Society, January, 1951.

3. DeBakey, M. E.: Military Surgery in World War II: Backward Glance and Forward Look, New England J. Med. **236**:341-350, 1947.

tate the presence of a well-trained vascular surgeon near the front lines. Gage [4] advocates immediate ligation of the severed artery to prevent hemorrhage and subsequent aneurysm, followed by blocking of the regional sympathetic ganglions with procaine for 10 days to keep the collateral arterial bed widely dilated.

COLLATERAL ARTERIAL CIRCULATION

If an aneurysm appears after any injury to a major peripheral artery, it has been customary to delay definitive treatment for three to six months while an adequate collateral arterial circulation developed spontaneously. This circulation can be enhanced by the use of the Matas compressor, digital pressure, passive vascular exercises with intermittent pressure and suction, sympathetic blocks, sympathectomies, or vasodilating drugs. The most effective method of bringing about maximal vasodilatation is by surgical sympathetic ganglionectomy before or immediately after the interruption of large arteries. For many years Leriche,[5] White,[6] and others have advocated sympathectomy for this purpose. Shumacher [7] reported a series of cases in 60% of which there was response to sympathectomy. The efficiency of the existing collateral arterial circulation can be estimated by the temperature and color of the skin of the distal parts of the extremity while the artery proximal to the aneurysmal sac is temporarily occluded. Arteriography is of little added value and may cause serious complications. Maximal vasodilatation is important for the restoration of adequate circulation through collateral pathways.

OPERATIVE TECHNICS

Spontaneous cure of an arterial aneurysm by thrombosis is rare; consequently, operative treatment is usually necessary. If surgical intervention is delayed, local pressure changes with pain, secondary hemorrhage, or arterial insufficiency of the distal parts with gangrene of the extremity may result.

Operative treatment for arterial aneurysms had its birth in the third century after Christ, when Antyllus ligated the main artery above and below an aneurysm and then opened the sac and packed it with a piece of cloth. In 1710 Anel ligated the artery proximal to the sac (Fig. 1*A*). The criticism of this method is that the aneurysm persists or recurs because of reestablishment of the circulation through the collateral arteries entering the sac. The superior, middle, and inferior genicular arteries may continue to feed blood into the aneurysmal sac, but this is not always the case since the cure of arterial aneurysms has followed simple ligation of the proximal artery. On the Vascular Service at the Cincinnati General Hospital, four arteriosclerotic fusiform aneurysms were treated by ligation of the proximal artery

4. Gage, M.: Traumatic Arterial Aneurysms of the Peripheral Arteries, Am. J. Surg. **59**:210-231, 1943.

5. Leriche, R.: Du rôle de l'innervation pariétale des artères et du sympathique dans le rétablissement de la circulation collatérale après oblitération ou ligature, d'après les recherches expérimentales de P. Stricker et F. Orban, Bull. et mém. Soc. nat. chir. **56**:657-664, 1930.

6. White, J. C.: The Autonomic Nervous System, ed. 2, New York, The Macmillan Company, 1944.

7. Shumacher, H. B., Jr.: Sympathectomy as an Adjuvant in the Operative Treatment of Aneurysms and Arteriovenous Fistulas, Surgery **22**:571-596, 1947.

alone. In three of the cases the aneurysms were cured, and in one the pulsation in the sac returned. Ligation of the incoming artery at a higher level was then done, and all pulsations in the aneurysm disappeared. Matas [8] reported an incidence of gangrene of 10.5% when this method was utilized. In his experience the Hunterian operation, in which the ligature is placed at some distance proximal to the aneurysmal sac, caused gangrene in the distal parts of the limb in 8.3% of cases. However, most of these reports antedate the methods which we now consider as effective stimulants to collateral arterial circulation or preventives of intravascular thrombosis. Figure 1*B* illustrates the ligation of the outgoing artery, a procedure that has been advocated but which we do not recommend. Ligation of the proximal and distal arteries was first described by Pasquin (Fig. 1*C*). One inactive syphilitic popliteal aneurysm of the fusiform type was treated in this manner at the Cincinnati General Hospital, and permanent obliteration of the aneurysmal sac resulted. Aneurysmectomy (Fig. 1*D*) with ligation of the incoming and outgoing major

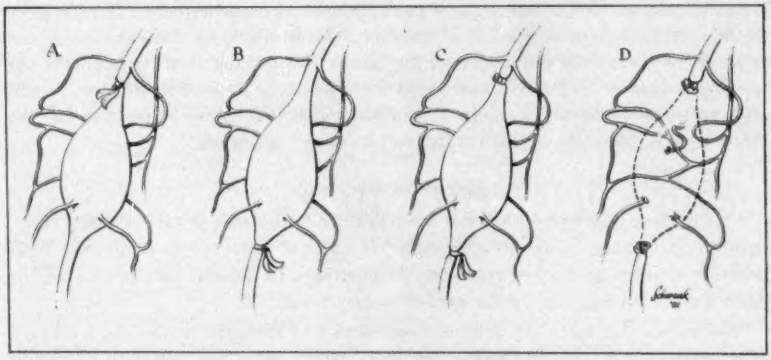

Fig. 1.—Drawings of the various extrasaccular methods of treating fusiform aneurysms of the popliteal artery.

arteries was first done by Purmann. We believe that such extensive surgery interferes with the collateral arterial pathways. Matas [8] reported 5.71% incidence of gangrene of the toes when this type of operation was performed. Small traumatic aneurysms of one of the paired arteries (radial or ulnar, anterior tibial or posterior tibial) can be successfully resected without danger of subsequent serious arterial insufficiency. These arteries are too small to permit satisfactory reconstruction.

The first major advancement in the surgery of aneurysms was the operation of endoaneurysmorrhaphy described by Matas [8] in 1888. It may be performed in three different ways. Figure 2*C* shows a fusiform aneurysm with all the arterial openings obliterated by sutures from within the sac. In restorative or reconstructive endoaneurysmorrhaphy of saccular aneurysms (Fig. 2*D*), Matas [8] in 1920 reported an incidence of gangrene of the limb of 5.71%. In 1949 Linton [9] reported 14 patients

8. Matas, R.: Surgery of the Vascular System: Aneurysms, in Keen's Surgery, Philadelphia, W. B. Saunders Company, 1909, Vol. 5. pp. 216-350.

9. Linton, R. R.: The Arteriosclerotic Popliteal Aneurysm, Surgery **26**:41-58, 1949.

in whom restorative endoaneurysmorrhaphy was done with simultaneous ligation of the concomitant vein and lumbar sympathetic ganglionectomy. The ideal method should not only maintain adequate arterial blood supply to the distal parts of the limb but should also permanently cure the aneurysm.

Recently, much has been written about the experimental methods of restoring the continuity of large arteries by excision of the aneurysmal sac and the performance of end-to-end arterial anastomosis (Fig. 3*A-D*) or by bridging the gap with autogenous venous grafts or preserved arterial isografts. There is still much to be desired from the use of isografts for replacement of peripheral arteries. In arterial surgery, exogenous materials are less desirable than autogenous grafts in man. Blakemore [10] revised the procedure of aneurysmectomy by bridging the defect with a segment of vein within a vitallium tube or by the use of small collars of vitallium to facilitate end-to-end anastomosis by the nonsuture method. Four cases showed satisfactory results after a short follow-up. Murray [11] pointed out that the difficulty

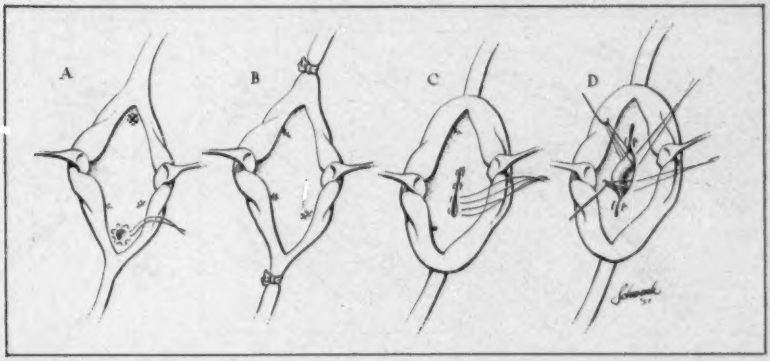

Fig. 2.—Drawings of the various intrasaccular methods of treating aneurysms of the popliteal artery.

with such anastomoses is not secondary hemorrhage, dilatation, or stenosis of the venous graft but actual obliteration of the segment by thrombosis. He found that 80% of arterial anastomoses will remain patent if sufficient heparin is given by continuous intravenous drip to maintain a clotting time two to three times of normal for three days after operation. When grafts of vein are used, seven days of heparinization are necessary to prevent thrombosis at the site of the anastomoses.

The method now being utilized at the Cincinnati General Hospital for treatment of fusiform aneurysms resulting from disease consists of the extrasaccular ligation of the proximal and distal arteries, with suture of the collateral arteries from within the sac. In order not to interfere with the collateral arterial pathways about the aneurysm, it is usually necessary to occlude temporarily all the blood vessels to the

10. Blakemore, A. H.: Restorative Endo-Aneurysmorrhaphy by Vein Graft Inlay, Ann. Surg. **126**:841-849, 1947.

11. Murray, G.: Heparin in Surgical Treatment of Blood Vessels, Arch. Surg. **40**:307-325 (Feb.) 1940.

extremity by a properly placed pneumatic cuff which when inflated serves as a tourniquet. The aneurysmal sac can then be opened and, after the clots have been removed, the incoming major artery can be located by gently inserting the end of a curved Kelly clamp into it. With the clamp in place the artery is then exposed by careful extrasaccular dissection. The outgoing artery is located in like manner, and the Kelly clamp is used as a guide for the extrasaccular exposure and ligation of this artery. The pneumatic cuff is then deflated, and the collateral arteries in the wall of the aneurysmal sac are located and closed by mattress sutures of silk from within the sac. When all bleeding has been controlled, the wall of the aneurysmal sac is allowed to fall together without sutures. The wound is then closed in layers. An adequate collateral arterial circulation to the distal parts of the extremity is essential to the success of this type of operation for the obliteration of arterial aneurysms.

Emphasis must be placed on the ligature material and on the method of application (Fig. 3*G-K*). In 1916 Halsted and Reid [12] repeated the experiments of

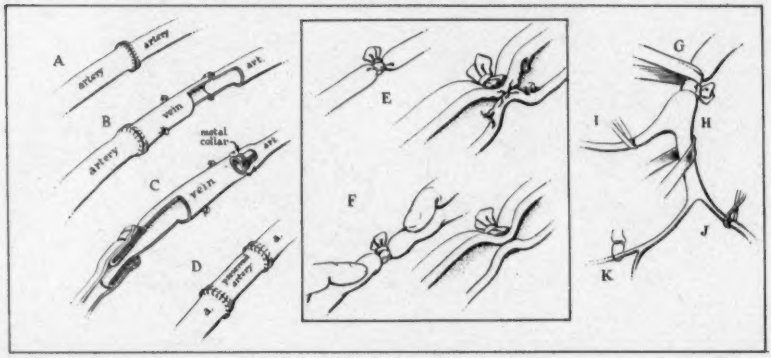

Fig. 3.—Drawings to illustrate principles of surgery of large arteries. *A—D*, methods of restoring continuity of large arteries; *E—F*, methods of ligating large arteries; *G—K*, size of ligature material for various-sized arteries.

Ballance and Edmunds [13] and concurred in their conclusions that complete occlusion of a large artery is dependent on the rapidity of the ingrowth of fibrous tissue into the ischemic segment included in the ligature. Thus if a large segment is included in a cotton tape approximately one half as wide as the diameter of the vessel, the rate of necrosis will be slower and a more complete replacement of the ischemic segment by fibrous tissue will take place. Any ligature that is too narrow will cut through the wall of the artery, and absorbable ligatures tend to loosen before

12. Halsted, W. S.: Experimental Study of Circumscribed Dilation of Artery Immediately Distal to Partially Occluding Band, and Its Bearing on Dilation of Subclavian Artery Observed in Certain Cases of Cervical Rib, J. Exper. Med. **24**:271-286, 1916. Reid, M. R.: Partial Occlusion of Aorta with Metallic Band: Observations on Blood-Pressures and Changes in Arterial Walls, ibid. **24**:287-290, 1916.

13. Ballance, C. A., and Edmunds, W.: The Ligation of the Larger Arteries in Their Continuity, Tr. Med. Chir., London **59**:443, 1886.

the segment has been replaced by fibrous tissue. The degree of damage to the coats of the artery at the time of ligation is in direct proportion to the speed and force used in tying the knot (Fig. 3*E-F*). Cellophane of special chemical composition can be recommended for gradual occlusion of large arteries. Its greatest usefulness is in the treatment of abdominal and thoracic aneurysms when complete extirpation or immediate obliteration of the sac is considered unwise.

SUMMARY

In this review it has been our desire to call attention to the various operative procedures that are being used for the treatment of peripheral arterial aneurysms and to emphasize those methods which are based on sound surgical principles. With all the supportive measures available today for the stimulation of collateral arterial circulation and the prevention of intravascular thrombosis, the surgical cure of peripheral aneurysms should become increasingly great, and as a result of newer technical methods the interruption of large peripheral arteries should give rise to fewer complications than at any other time in the long history of vascular surgery.

LEG AND THIGH AMPUTATIONS IN OBLITERATIVE ARTERIAL DISEASE

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UNTIL the past few years major amputation in obliterative arterial disease has been associated with a distressingly high mortality. As recently as a decade ago, published figures ranged from 13 to as high as 80%.[1] In 1940, Veal[2] remarked that the "mortality rate for amputation of a lower limb for vascular gangrene has remained excessively high, although it was one of the earliest major operations to be performed. Even the introduction of aseptic surgical technique and safe anesthetic agents has failed to reduce this rate in proportion to most other standard operations."

During this period most of the major amputations in the lower extremity were carried out through the thigh, and, to be sure, the same policy is generally followed at the present time. There have been, of course, exceptional surgeons, such as Maes,[3] who some years ago recommended closed amputations below the knee. The Council on Physical Therapy of the American Medical Association, however, expressed the attitude of most surgeons when, in 1941, it warned against the use of leg amputations and cautioned that this operation should be restricted to a select group of patients and to those in whom a good popliteal pulsation was present. The members of the Council also felt that only the most experienced surgeons should attempt amputations below the knee. The availability of chemotherapeutic agents and antibiotics, as well as improved methods of preoperative preparation of the extremity,[3a] has served as an incentive for trial of more amputations at a lower level in the hope of lowering the mortality and increasing the use-

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Before July 1, 1948, the patients were treated in the New Haven Hospital and after that date at the Indiana University Medical Center.

1. (*a*) Amputations in Diabetes Mellitus and Peripheral Vascular Diseases, report of the Council on Physical Therapy, Ch. 4, J. A. M. A. **117**:1095 (Sept. 27) 1941. (*b*) Silbert, S., and Haimovici, H.: Results of Midleg Amputations for Gangrene in Diabetics, J. A. M. A. **144**:454 (Oct. 7) 1950.

2. Veal, J. R.: High Ligation of the Femoral Vein in Amputations of the Lower Extremities, J. A. M. A. **114**:1616 (April 27) 1940.

3. Maes, U.: The Surgery of the Diabetic as It Concerns Gangrene of the Lower Extremities and Carbuncles, Surg., Gynec. & Obst. **51**:700, 1930.

3a. Allen, F. M.: Experiments Concerning Ligation and Refrigeration in Relation to Local Intoxication and Infection, Surg., Gynec. & Obst. **68**:1047, 1939.

fulness of the stump. Silbert and Haimovici [1b] have reported good results with leg amputations, and McKittrick and his associates [4] have demonstrated that satisfactory results can be achieved in certain cases with transmetatarsal amputation. Regardless of the level of amputation, it seems clear that the chemotherapeutic and antibiotic agents are influencing the outcome favorably. Perlow and Roth,[5] for example, reported a decrease in the mortality following major amputations from 25% in the period 1936 to 1938 to 11.7% in the period 1945 to 1947, during which penicillin was used.

It is the purpose of this communication to discuss our experiences with 128 consecutive leg and thigh amputations performed on 113 patients with obliterative arterial disease from October, 1946, to Feb. 1, 1951. Sixty-four of the patients had diabetes as well as arteriosclerosis, 45 had arteriosclerosis, and four had thromboangiitis obliterans. In the diabetic group there were 36 women and 28

TABLE 1.—*Age Distribution of Patients with Arteriosclerosis and Diabetes Requiring Major Amputation*

Disease	Age					
	41-50	51-60	61-70	71-80	81-90	Average
Arteriosclerosis	1	8	8	20	8	71.4
Diabetes	7	6	37	9	5	64

TABLE 2.—*General Condition of Patients Before Amputation*

Disease	General Condition			
	Good	Fair	Poor	Precarious
Arteriosclerosis	5	15	16	9
Diabetes	8	33	17	6
Thromboangiitis obliterans	1	1	2	0

men, while 35 of those with arteriosclerosis alone were men and only 10 women. All four of the patients with thromboangiitis obliterans were men. Most of the patients (77%) were over 60, and 37% were over 70 yr. old. In the diabetic group 51 of the 64 patients were over 60, 14 over 70 and five over 80; the average age was 64 (Table 1). The arteriosclerotic group without diabetes was older, averaging 71.4 yr. Thirty-six of the 45 patients were more than 60, 28 more than 70 and eight more than 80 yr. old. The four patients with thromboangiitis obliterans were younger, their ages ranging from 26 to 53 and averaging 41.2 yr.

When the general condition of the patients before operation was judged as objectively as possible and such factors as age, cardiovascular status, and renal function were taken into consideration, only 14 of the 113 patients were felt to be in good condition (Table 2). Forty-nine were thought to be in fair condition, 35 in poor condition and 15 in a precarious state. The level of the main arterial occlusion, as determined by palpation of pulses and oscillometry (Table 3), was in

4. McKittrick, L. S.; McKittrick, J. A., and Risley, T. S.: Transmetatarsal Amputation for Infection or Gangrene in Patients with Diabetes Mellitus, Ann. Surg. **130**:826, 1949.

5. Perlow, S., and Roth, H. A.: Amputation for Gangrene Due to Occlusive Arterial Disease, Surgery **25**:547, 1949.

the femoral artery or higher in 85 patients. In 10 patients the popliteal artery was occluded, and in 18 the level of occlusion was distal to the popliteal artery. All the patients had well established gangrene or ulcerated areas resulting from gangrene. In all but 13 patients there was present infection of some degree, ranging from localized cellulitis or a small abscess beneath a necrotic eschar to extensive cellulitis of the foot and leg associated with lymphangitis.

By the time most of the patients came under our care the local condition was such as to make it apparent that nothing short of a major amputation would suffice. In the exceptional cases every effort was made to conserve the limb. The circulatory status was carefully evaluated, the affected foot was kept in the position of optimal blood flow, somewhat below the level of the heart, the foot was carefully cleansed and kept in sterile dressings, foot boards were used to prevent pressure on the toes from bed clothes, and necrotic tissue was carefully removed through the line of demarcation. Antibiotics were given whenever infection was present —penicillin as a general rule and streptomycin in some instances. In addition, sterile saline compresses kept at body temperature were used alternately with dry or petroleum jelly dressings as necessitated by softening of the skin and the threat of

TABLE 3.—*Level of Main Arterial Occlusion*

	Level of Occlusion				
Disease	Aorta	Iliac	Femoral	Popliteal	Below Popliteal
Arteriosclerosis	1	8	30	2	3
Diabetes	0	5	28	7	15
Thromboangiitis obliterans	0	0	3	1	0

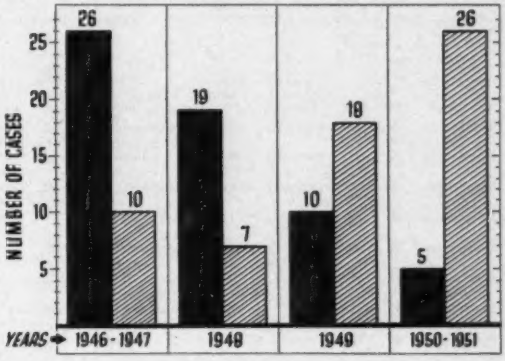
maceration. In 12 cases an extensive local débridement or amputation of digits was carried out. In three instances unsuccessful transmetatarsal amputations preceded the final major amputation. In 25 cases careful studies of the vasomotor response to sympathetic, spinal or peripheral nerve block were made, and in 11 cases lumbar sympathectomy was performed from a few days to several months before amputation was carried out.

Whenever infection was present and was not apparently brought under good control by local measures and antibiotics, the infected foot was removed surgically or was excluded by tourniquet and refrigeration. In 10 cases an open amputation through the supramalleolar area was performed from about five to 10 days before definitive amputation. Most of the procedures were carried out under local infiltration anesthesia. In 40 cases the foot was refrigerated and a tourniquet placed about the leg for two to four days before amputation. Every effort was made to bring any existing diabetes under the best possible control.

Spinal anesthesia was considered the anesthesia of choice and was used for 101 of the operations. Generally an effort was made to obtain anesthesia in one leg, and success was ordinarily achieved. Depending on the patient's age and size, from 4 to 10 mg. of powdered tetracaine (pontocaine®) hydrochloride was used, being dissolved, as a rule, in 1 cc. of spinal fluid, 1 cc. of a solution of epinephrine or ephedrine, and 1 cc. of 10% dextrose. The solution was injected in the fourth interspace with the patient lying on his side and with the affected extremity down.

After injection the foot of the table was lowered and the patient kept on his side for 15 to 20 min. There was always good anesthesia of the involved extremity and generally little or no fall in blood pressure. The amputation was carried out with the patient supine. The leg and thigh were generally prepared and draped out so that a thigh amputation could be performed if the circulation were judged inadequate for a leg amputation.

In the case of the leg amputations, short anterior and posterior flaps of approximately equal length were used. In general, longer anterior and shorter posterior flaps were employed in thigh amputations. Some of the low thigh amputations were performed according to the technique of Callander. The other amputations were carried out more or less according to the classical methods. In no case was a tourniquet used. In the leg amputations the fibula was divided with a Gigli saw. Great care was taken to achieve complete hemostasis, and the wounds were thoroughly irrigated with isotonic sodium chloride solution. Every effort was



Changes in sites of primary amputations by years. Solid bars indicate thigh amputations and lined bars, leg amputations.

made to avoid traumatizing the tissues; the skin was approximated without the use of forceps in order to obviate any necrosis which might result from their use. Fine black silk ligatures and sutures were used throughout. None of the wounds was drained, and the skin edges were brought together with especial care. The major nerves were treated by ligation and high division. Muscles and tendons were sectioned in such a fashion as to obtain a slightly conical stump. Dry dressings were secured in place with a gently applied elastic bandage. A posterior splint was used in the case of leg amputations.

Generally, in the absence of anything suggesting difficulty with the stump, the first dressing was done from the 8th to the 10th postoperative day and sutures were removed in stages between the 13th and the 15th days. Ordinarily the patients were discharged on the 15th postoperative day.

Of the 128 amputations performed, 121 were carried out as primary definitive procedures, while seven were reamputations necessitated by difficulty with the first amputation stump. Sixty-one of the primary operations were leg amputations, 53

were supracondylar amputations, of which 31 were done according to the technique of Callander, and 7 were midthigh amputations. Four of the reamputations were open amputations, three through the midthigh and one through the supracondylar region. Two were closed midthigh and one a closed supracondylar amputation. During the period covered by this survey, there has been a progressive tendency toward the use of leg amputations in preference to thigh amputations (chart). Until Jan. 1, 1949, only 17 of 62 primary amputations were carried out below the knee while during the subsequent two years 44 of 59 amputations were through the leg. The great majority of the amputations were done by the members of the resident house staff, usually by the junior residents.

Twenty of the 113 patients either had undergone major amputation of one lower extremity prior to being seen or had required major amputation of both lower extremities at some time during the four years of this study. Fifteen of these bilateral amputees were diabetics; the other five suffered from arteriosclerosis.

TABLE 4.—*Postoperative Deaths*

Disease	Preoperative General Condition	Age	Sex	Level of Arterial Occlusion	Infection in Foot	Type of Amputation	Death	
							Day After Operation	Cause
Diabetes	Precarious	64	F	Femoral	4+	Supracondylar	7	Mesenteric thrombosis
Diabetes	Precarious	65	M	Femoral	2+	Leg	2	Coronary thrombosis
Arteriosclerosis	Precarious	66	M	Femoral	2+	Supracondylar	23	Cerebrovascular accident
Arteriosclerosis	Precarious	82	M	Femoral	3+	Leg	2	Congestive heart failure
Arteriosclerosis	Precarious	73	M	Below popliteal	3+	Supracondylar	27	Ruptured left ventricle
Arteriosclerosis	Poor	79	M	Femoral	1+	Leg	1 hr.	Cerebrovascular accident
Arteriosclerosis	Poor	73	M	Iliac	None	Supracondylar	12	Cerebrovascular accident
Thromboangiitis obliterans	Poor	53	M	Femoral	None	Leg	5	Coronary thrombosis

There were eight deaths in the series (Table 4). Two of those who died were diabetics, 5 patients with arteriosclerosis without diabetes, and one a patient with thromboangiitis obliterans. With the exception of the latter patient, all were 64 yr. or more in age, and four were 73 or older. The general condition before operation was judged to be precarious in five and poor in the other three. Two of them, for example, were semicomatose on their admission, one had had fibrillation and severe cardiac failure for three years, one had had a cerebrovascular accident a few months before as well as having had obvious heart disease, and two had old coronary artery disease. All eight died of some cardiovascular accident. Two died of coronary thrombosis, one of congestive heart failure, one of a ruptured left ventricle, and three of a cerebrovascular accident, and one apparently died of acute mesenteric thrombosis. Autopsies were performed on five and in all except one of the other three the cause of death was reasonably clear from the clinical observations.

Four deaths followed leg amputation, making the mortality from this procedure 6.6%. Four deaths followed low thigh amputations. The mortality rate from all thigh amputations was 6%. The over-all operative mortality was 6.25%. There were two deaths in 74 amputations on diabetics, or a mortality rate of 2.7%, five deaths in

50 operations on patients with arteriosclerosis without diabetes (10%), and one death in four amputations for thromboangiitis obliterans.

There was some difficulty with healing of the stump in 14 of the 58 patients who survived amputation through the leg for a long time (Table 5). In nine, though healing was delayed somewhat, reamputation was unnecessary. In one the wound was disrupted by a fall from bed and had to be resutured. In two, minor revision was required as the result of a small area of necrosis, and in a third a small skin defect resulting from a wound infection was covered with a split thickness graft. In the other 5 cases the stump healed without any additional surgical procedure. In five of these patients, however, reamputation was necessary. Tragically enough, no difficulty should have occurred in three of them. Two patients fell out of bed, struck the stump, which was nearly completely healed, and injured it irreparably. In another patient the stump looked well healed on the 13th day. On the following day it was also irreparably injured by self-inflicted trauma. Infection was respon-

TABLE 5.—*Wound Complications Following Closed Amputation*

Disease	Type of Amputation	Number of Operations*	No. with per Primam Healing	No. with Impaired Healing Due to Trauma	No. with Infection or Hematoma	No. with Necrosis of Wound Edges	No. Requiring Reamputation
Diabetes	Leg	40	31 (78%)	3	3	3	2
	Callander	18	14 (78%)	0	2	2	0
	Classical supracondylar	11	11	0	0	0	0
	Midthigh	5	5	0	0	0	0
Arteriosclerosis	Leg	16	11 (69%)	1	1	3	2
	Callander	12	9 (75%)	0	3	0	1
	Classical supracondylar	10	10	0	0	0	0†
	Midthigh	6	6	0	0	0	0
Thromboangiitis obliterans	Leg	2	2	0	0	0	0
	Callander	1	1	0	0	0	0
All	Leg	58	44 (76%)	4	4	6	5
	Callander	31	24 (78%)	0	5	2	1
	Classical supracondylar	21	21	0	0	0	0†
	Midthigh	9	9	0	0	0	0

* Patients not surviving 12 days or more are excluded.
† One patient underwent reamputation for painful adherent scar six months after primary operation.

sible for the failure in one case and necrosis of the skin edges in one. In summary, the difficulty with healing in four of the patients was solely the result of trauma, in four the result of infection, and in six the result of varying degrees of necrosis of the skin edges.

Thirty-one patients survived a Callander amputation for a long time. There was some difficulty with wound healing in seven, in five the result of hematoma and/or infection and in two the result of small areas of necrosis of the skin. Healing took place without additional surgical intervention in all except one patient in whom reamputation was necessary. No immediate difficulty followed classical supracondylar or midthigh amputation in the 30 patients who survived these procedures for 12 days or more. However, one patient who had a supracondylar amputation underwent a reamputation six months later because of a painful adherent scar.

Of the 21 patients who had some delay in wound healing, minor surgical procedures were necessary in four and reamputation in six. If trauma to the stump had been avoided, however, only three amputations would have been required because of inadequate healing of the stump.

COMMENT

This study, like several others recently made,[6] demonstrates the fact that major amputations for gangrene resulting from obliterative arterial disease and diabetes can be carried out with reasonable safety. The over-all mortality rate was 6%. It is of interest that five of the eight patients who died were thought to be in a precarious condition before operation and the other three in poor condition. Excluding those patients whose preoperative condition was obviously precarious, 113 amputations were performed in 98 patients, with three postoperative deaths, an operative mortality of 2.7%. It is of further interest that all of the deaths were apparently the result of cardiovascular difficulties.

There were no deaths in this series from infection, shock or pulmonary embolism, complications which accounted for a significant proportion of deaths in the past.[7] In considering possible factors involved in the reduction of fatal postoperative complications, one must, of course, regard the use of penicillin and other antibiotics as of prime importance. Preoperative exclusion of the infected foot either by guillotine amputation above the ankle or by tourniquet and refrigeration is also obviously a very important measure. Other factors which we feel are important include proper regulation of diabetes if present, the use of one-leg spinal anesthesia, early ambulation and supervised exercise of the extremities in bed, the avoidance of shock, adequate fluid replacement, and rigid adherence to the principles of gentleness in handling tissues and of careful hemostasis.

In this series there was no difference in mortality between leg and thigh amputations. The over-all mortality rate was somewhat greater (10%) in patients with arteriosclerosis than in those with diabetes (2.7%). This difference is likely related to the fact that the arteriosclerotic group were, on an average, 7.4 years older than the diabetic group and presumably were more susceptible to the cardiovascular complications which were responsible for all eight of our fatalities.

Wound complications were encountered more frequently in leg amputation than in thigh amputations. However, the difference, as far as serious difficulty is concerned, is more apparent than real. In the case of leg amputations, three otherwise viable, well-healed stumps were irreparably ruined by trauma, which certainly should be avoidable as a causative factor. If the figures for necessary reamputations could be corrected accordingly, two reamputations would have been required following 61 primary closed leg amputations and two reamputations following 63 closed midthigh and low thigh amputations.

It is our conviction, furthermore, that in the future we should be able to reduce substantially the incidence of wound complications. Experiences to date have emphasized the importance of closing the stumps with loose skin flaps. In some of our cases it is apparent in retrospect that the flaps were not loose enough at the time of closure, a failure much more often due to insufficient conical resection of the large muscle masses, especially in leg amputations, than to insufficient resection of bone. Our experiences have also convinced us that tourniquet and refrigeration should be used more extensively than was done during the early years of this study. Their use should be extended to cases of moderate or even minimal infection. The relative merits of guillotine amputation above the ankle and of tourniquet and

6. Perlow and Roth.[5] Silbert and Haimovici.[1b]

7. Veal, J. R.: Factors in the Mortality Rate of Arteriosclerotic Gangrene, J. A. M. A. **110**:785 (March 12) 1938.

refrigeration in case of serious infection must be established by more experience. Closer supervision and better nursing care should make it possible to avoid injury to the healing stump, which was responsible for difficulty with the wound in four of our cases.

Our series is too small to permit any far-reaching conclusions. At the present time we feel justified, however, in continuing to carry out leg amputation by preference. The leg stump is a particularly comfortable stump. It is easily fitted with a prosthesis and provides good knee action. Furthermore, it adds considerably to the patient's stability even if he becomes confined to a wheel chair or, for that matter, bedridden. In our own series, 20 patients have already undergone bilateral amputation, a possibility which increases each year the patient survives. Pulsation in the popliteal artery is not necessary for a successful leg amputation. In only 16 of our 61 cases of leg amputation was a popliteal pulsation present. In 5 the line of occlusion was popliteal, in 30 femoral, and in 10 iliac. The principal contraindications to amputation below the knee are severe flexion contractures at the knee, gangrene or infection extending proximally up to the desired level of amputation, and inadequate blood supply. The policy of draping the extremity so that amputation can be carried out either through the leg or thigh and of using the gross vascularity noted on trial incision into the leg as the principal guide to adequacy of circulation is very helpful. It is more reliable, we find, than any method of preoperative evaluation.

Our experiences suggest that better results are obtained when supracondylar amputations are carried out in the more or less classical manner than when they are done by the Callander technique, though the numbers of patients treated are too few to permit rigid conclusions. Although we have generally used longer anterior and shorter posterior skin flaps in thigh amputations, it is evident that flaps of more equal length should be used if there is any doubt whatsoever concerning their viability. With modern prosthesis a well-healed scar over the end of the stump is generally satisfactory, provided the stump is otherwise a satisfactory one.

Lumbar sympathetic denervation is of real value in the prevention of gangrene and in the healing of superficial necrosis and ulceration. It is undoubtedly also a useful procedure in certain cases as a measure to make a successful amputation at a low level more likely. In the presence of well-established gangrene and infection which obviously commits one to a major amputation, as was the case in most of our patients, sympathectomy would not often seem a justifiable procedure.

SUMMARY

Experiences with 128 major amputations performed on 113 patients suffering from obliterative arterial disease are analyzed. Factors concerned with preoperative, operative, and postoperative management, mortality, difficulties with proper healing of stumps, and the choice of level of amputation are discussed.

GASOMETRIC STUDIES IN CAROTID-INTERNAL JUGULAR ANASTOMOSIS IN THE NECK

Preliminary Report on Human Experiences

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DETROIT

THE USE of cervical carotid artery-internal jugular vein anastomosis as a means of revascularizing the brain has been championed by Beck, McKhann, and Belnap.[1] Experimental work in the rhesus monkey [2] revealed that such an anastomosis does not result in increase in the oxygen content of the superior-sagittal sinus blood; in many of the experiments the oxygen content of the superior sagittal sinus blood is actually lower after the shunt. Angiographic studies in the rhesus monkey after a shunt reveal that blood usually courses up one jugular vein to the lateral sinus and across to the opposite lateral sinus and down the contralateral jugular vein or it courses through the tributaries in the neck to the opposite jugular vein. Tarlov and others [3] found that in carotid artery-internal jugular vein shunts in human beings the postoperative angiographic pattern is essentially the same as the results of the above-described work in the rhesus monkey. They conclude that most of the blood courses up the jugular vein on the side of the shunt, through the lateral sinus, to the lateral sinus on the opposite side, and down the contralateral jugular vein.

In a recent paper by McKhann, Belnap, and Beck [4] only a passing comment has been made on the fact that following such a shunt in human beings the oxygen

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From Department of Neurosurgery, Wayne University College of Medicine, Grace Hospital.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1951.

1. Beck, C. S.; McKhann, C. F., and Belnap, W. D.: Revascularization of the Brain Through Establishment of a Cervical Arterio-Venous Fistula, J. Pediat. **35**:317-329, 1949.

2. Gurdjian, E. S.; Webster, J. E., and Martin, F.: Carotid-Internal Jugular Anastomosis in the Rhesus Monkey: Angiographic and Gasometric Studies, J. Neurosurg. **7**(No. 6):467-472, 1950.

3. Tarlov, J. M.; Shure, B.; Epstein, B. S.; Hirsch, E., and Nissen, R.: Brain Revascularization After Carotid-Jugular Anastomosis Assessed by Angiography, Arch. Neurol. & Psychiat. **64**:847-860 (Dec.) 1950.

4. McKhann, C. F.; Belnap, W. D., and Beck, C. S.: Cervical Arterio-Venous Anastomosis in Treatment of Mental Retardation, Convulsive Disorders, and Cerebral Spasticity, Ann. Surg. **132**:162-175, 1950.

per cent saturation of the superior sagittal sinus is definitely increased. It was felt that careful gasometric studies in human beings were indicated in order to evaluate conflicting opinions and also to correlate experimental findings and findings in human beings. Our present paper is a study of five patients with cervical arteriovenous shunt, studied by angiography and by the oxygen content in the various vessels involved.

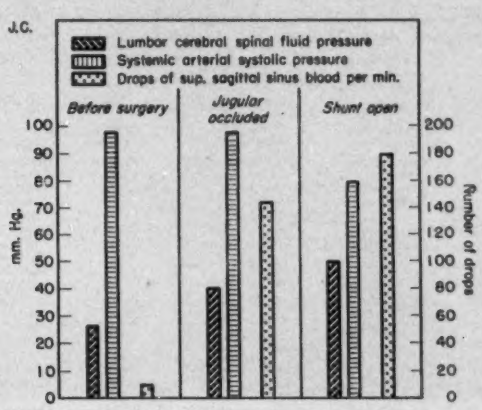

Fig. 1.—Spinal-fluid pressure before shunt, with jugular vein occluded, and after shunt, in millimeters of mercury. The number of superior-sagittal-sinus blood drops a minute before shunt, with jugular vein occluded, and after shunt.

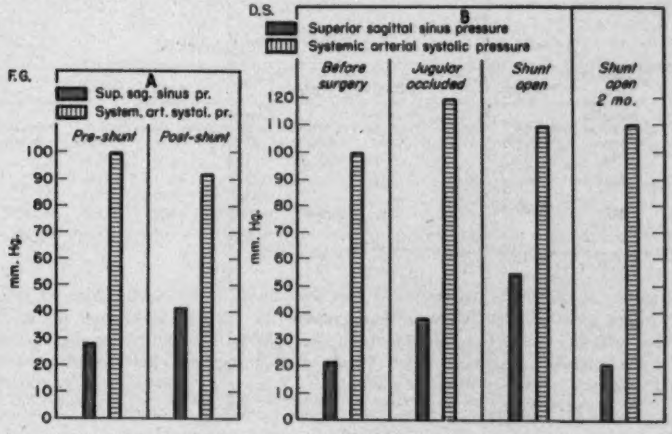

Fig. 2.—*A*, superior-sagittal-sinus and arterial systolic blood pressures before and after shunt. *B*, superior-sagittal-sinus and arterial systolic blood pressures before shunt, with jugular vein occluded, with shunt open, and two months after shunt. Note return of pressure to preshunt level.

TECHNIQUE

Two teams working together made it possible to obtain the data effectually without lengthening the time of operation. One group worked upon the neck and estabiished a communication between the common carotid artery and the internal jugular vein, and another group worked

upon the head, exposing the sagittal sinus through a trephine opening, and obtained the various data, as well as the blood specimens for gasometric study. The pressure of the blood in the sagittal sinus before and after the shunt was recorded by counting the number of drops a minute from an 18-gauge needle introduced into the sinus toward the confluence (Fig. 1). In two patients the blood from the sagittal sinus was permitted to rise in a manometric tube treated with heparin sodium for recording of the pressure (Fig. 2). The spinal-fluid pressure also was studied by continuous recording during the operation. The collected blood specimens included carotid, jugular, and superior sagittal sinus blood. After the shunt, specimens were obtained from the area of the shunt, the sagittal sinus, and a systemic vein. The patients were administered 3,000 cc. of oxygen a minute under general anesthesia with an intratracheal tube.[5]

TABLE 1.—*Summary of Clinical Observations*

Case	Age	Sex	Indications for Shunt	Pneumoencephalogram	Shunt Status	Postshunt Results
J. C.	2½	M	Convulsions: 6-8/day Retardation Hyperkinesis	Cerebral atrophy: moderate	Patent 5 mo.	Convulsions decreased Patient quieter Right proptosis Enlargement of facial and scalp veins
F. G.	2	F	Convulsions Retardation	Porencephalia: rt. post. parietal Internal hydrocephalus Cerebral atrophy	Patent 3 mo.	Parents feel there is improvement in contact with environment Convulsions: same
D. S.	3	F	Convulsions Retardation Hyperkinesis	Normal	Patent 2 mo.	No clinical improvement noted Dilation of facial and scalp veins EEG: improvement
B. T.	7	F	Retardation Hyperkinesis Noisy	Brain atrophy: moderate	Patent 13 mo.	Less noisy Parents state patient is much improved
A. W.	1½	M	Severe birth injury Physical and mental retardation	Brain atrophy: moderate	Closed at surgery	Definite improvement in patient's contact with environment Parents feel patient definitely improved EEG: improved

TABLE 2.—*Oxygen Studies Before and After Shunt**

	Preshunt			Immediate Postshunt		Late Postshunt			
Case	Superior Sagittal Sinus	Carotid Artery	Jugular Vein	Superior Sagittal Sinus	Carotid Artery	Superior Sagittal Sinus	Peripheral Vein	Shunt	Peripheral Artery
J. C.	7.87	.....	.....	5.13	.....	5.49	15.70	13.10	.....
F. G.	11.05	16.50	10.00	11.40	.....	11.76	15.72	16.50	.....
B. T.	.....	.....	.....	.....	.....	10.80	15.50	12.96	.....
D. S.	12.98	17.00	.....	9.36	17.40	7.82	13.20	14.10	14.20

* All values are expressed in volumes per cent of oxygen.

In one patient (Case B. T.), gasometric studies were done several months after the shunt. In three patients, gasometric studies were done immediately and two weeks later the studies were repeated, with the specimens obtained percutaneously. In the fifth patient, the shunt became occluded at the conclusion of the operation. In all of these patients, electroencephalographic records were obtained before and after the shunt.

RESULTS

In Table 1 the age, sex, indication for operation, patency of the shunt, and results are shown for the five patients. In Table 2 the results of gasometric studies of carotid-artery, internal-jugular-vein, and sagittal-sinus blood oxygen content

5. Help was given by Dr. R. M. Johnston and Dr. H. J. Zukowski of the department of anesthesiology.

Fig. 3 (Case F. G.).—The pattern is typical, with no visualization of the sagittal sinus.

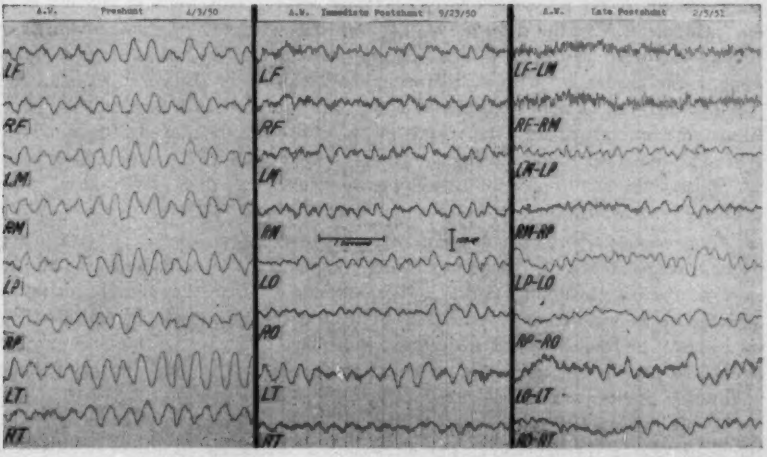

Fig. 4 (Case A. W.).—To the left is the generalized delta discharge. In the middle the record shows immediate postshunt findings of lowering of the voltage and increase in the frequency of the pattern. To the right, a more normal record for this age group is seen. Note that this record shows improvement between the first and second readings, which are five months apart, as well as between the second and third readings, which are also five months apart. These findings may represent a normal maturation process for this age group. The shunt in this baby became occluded before the end of the operation.

before and after the shunt are shown. For comparison, a peripheral vein was also used to note the degree of oxygenation that was possible on 3,000 cc. of oxygen a minute administered by the intratracheal route. It is interesting to note that the values of sagittal-sinus blood two weeks and longer after the shunt are essentially the same as those obtained immediately after the procedure. These findings are similar to those obtained in the rhesus monkey. The oxygen content of the sagittal-sinus blood is definitely lower than that of the blood in the region of the shunt and much lower than that of the blood obtained in a peripheral vein. It will be noted that the oxygen content of the blood from the region of the shunt is slightly higher than that of a peripheral vein in two cases and slightly lower in the remaining two. It is felt that this is due to the position of the needle in the shunt area. In Case F. G., two sets of angiograms were obtained because the first visualized the carotid artery, the needle end being in the carotid vessel. The specimen obtained from this needle showed a higher oxygen content than the peripheral vein. The needle was reintroduced later into the shunt area and the angiographic findings are shown in Figure 3.

Blood Pressure in the Sagittal Sinus.—The pressure of the blood in the sagittal sinus is definitely increased following the shunting procedure. Either by the drop method or by the method of actual manometric determination, the pressure of the sagittal sinus is seen to increase and the immediate postshunt pressure may be in the neighborhood of 40 mm. of mercury (Fig. 2). In all three cases recorded, the increase in the pressure of the sagittal-sinus blood following the opening of the shunt was associated with a slight decrease in the systemic systolic pressure. When the manometer is used for the recording of the sagittal-sinus blood pressure, one can actually see the pulsations of the blood in the manometer. By the drop method, it was shown that the number of drops a minute increased appreciably following the shunt (Fig. 1). Records were also kept of the change in pressure following the occlusion of the neck veins on the side operated on. These records may not be very accurate in that there may have been some pressure against the vessels on the opposite side as well; consequently, there may have been bilateral jugular compression rather than unilateral. In Case D. S., a three-month-postshunt manometric determination of the sagittal-sinus pressure revealed a return to the preshunt level.

Electroencephalographic Findings.—In all five cases, the electroencephalographic records showed changes following the shunt. These changes, as may be seen in the accompanying figures, were variable so that they are of doubtful significance in evaluating results. Generally, the changes were characterized by an increase in frequency and a decrease in voltage. The electroencephalographic alterations may be due to anoxia, effects of anesthesia, and, among the very young, maturation processes.

Of special interest is the record of A. W. whose shunt became occluded at the conclusion of the operation. The electroencephalographic record of this patient is shown in Figure 4. In this record, there was evidence of improvement between the first and second readings, which were five months apart, and the second and third readings, which were also five months apart. The second reading was immediately after the shunt. It is felt that the changes in these records may represent a normal maturation process for this 1½-yr.-old baby. Almost a similar pattern is noted in D. S., aged 3 years. The records in Figure 5 show that there was marked

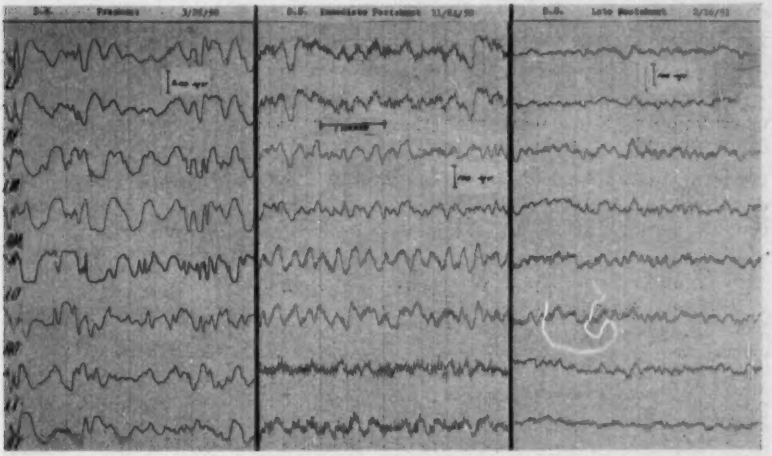

Fig. 5 (Case D. S.).—On the left is the electroencephalographic record seven months before the shunt, in the middle, the immediate postshunt record, and on the right, the three-month postshunt record. These records show marked improvement which may be another example of a maturation process for this age group.

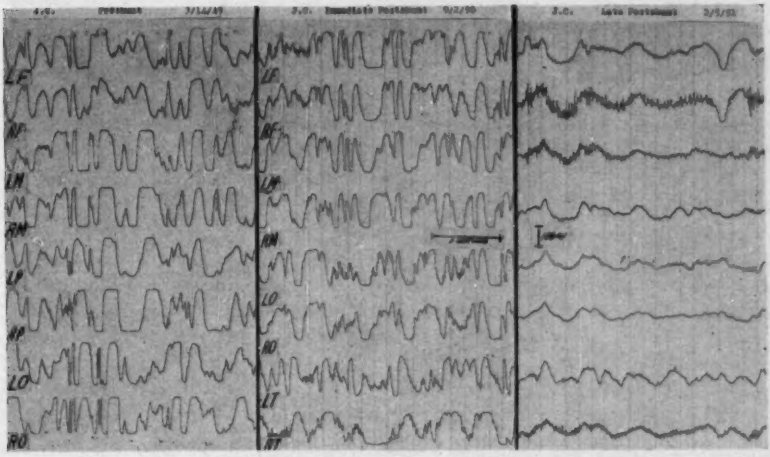

Fig. 6 (Case J. C.).—On the left is a marked convulsive pattern which was not bettered by the shunt, as shown in the middle record. On the right is evidence of severe brain disease from an electroencephalographic standpoint.

improvement three months after the shunt. There was also a definite improvement between the first record seven months prior to the shunt and the record immediately after the shunt. It should be remembered that in D. S. the shunt remained patent, whereas in A. W. the shunt closed at the conclusion of the operation.

In Case J. C. there was evidence of marked convulsive activity which persisted following the shunt (Fig. 6). In the record obtained four and a half months after the shunt, there was evidence of severe brain disease from an electroencephalographic standpoint (flattening and delta discharges). In Case B. T., the preshunt electroencephalogram showed an unspecific unstable pattern with delta discharges, whereas immediately following the shunt there was an increase in the delta activity as usually seen in severe brain injury. Twelve months later, the pattern had returned to its preshunt state (Fig. 7).

Fig. 7 (Case B. T.).—The preshunt electroencephalogram to the left shows a nonspecific unstable pattern with delta discharges. The middle record is immediately after the shunt. There is increased delta activity as usually seen in severe brain injury. On the right, the pattern has returned to its preshunt state.

Angiography.—Thirty-five per cent iodopyracet (diodrast®) was injected in amounts of 10 to 15 cc. into the shunted area, and x-ray exposure of one-fifth second was made simultaneously. The angiographic pattern was similar to that obtained in the rhesus monkey after a carotid artery-jugular vein shunt. The blood appeared to go up one jugular vein to the lateral sinus on the same side, thence to the lateral sinus on the opposite side, and down the contralateral jugular vein. All four patients had similar angiographic findings (Figs. 3, 8, and 9).

Clinical Data.—Among those patients in whom convulsive seizures were the feature of the disease, there was a cessation or lowering in the number of seizures following the shunt. In Case J. C. there was a beginning return of the convulsions four months after the shunt. The patients with hyperkinesis were much quieter after the operation. This was a welcome improvement, according to the

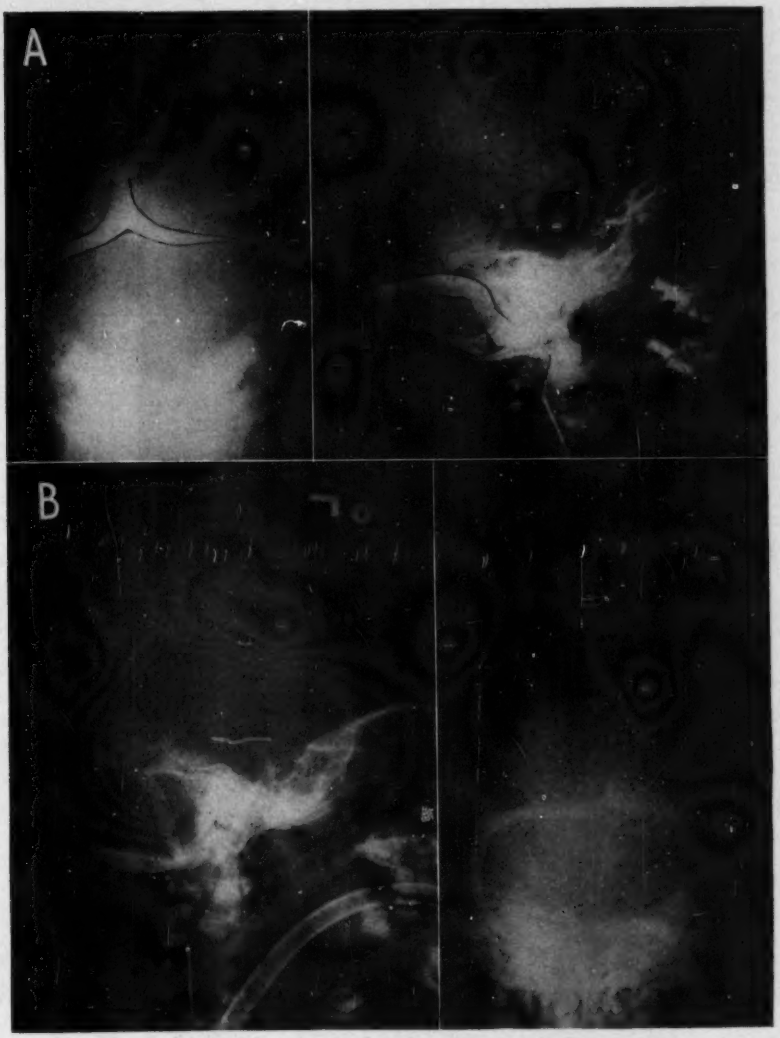

Fig. 8.—*A* (Case J. C.).—The posterior portion of the sagittal sinus is shown, but easy exit through the opposite lateral sinus and down the contralateral jugular vein is evident. *B* (Case D. S.), the pattern is typical, with dye traversing the lateral sinus to the jugular vein in the neck.

parents. In Cases J. C., D. S., and B. T. there were varying degrees of choked discs on the same side with little or no choking on the opposite side. In Case J. C. there was some proptosis of the right eye. In Cases J. C. and D. S., marked enlargement of the facial and scalp veins was observed. In Case J. C. a weak-

Fig. 9 (Case B. T.).—There is evidence of flow into the sagittal sinus.

Fig. 10 (Case F. G.).—Marked reduction in voltage in a three-month period following the shunt.

ness of the left half of the body also developed about a month following the shunt. A lumbar puncture was not done at the time of appearance of this weakness to note whether or not there was a cerebral hemorrhage such as was noted by Tarlov and others [3] in a similar case.

The bruit and thrill immediately over the area of the shunt persisted in all cases except one. In A. W., thrombosis probably occurred at the conclusion of the operation. The parents feel that there has been improvement in the general activity of the baby in its reaction to the environment.

A note should be made concerning the reaction of the parents to the patients' conditions as compared with the data obtained by the staff in follow-up studies. The reaction of the staff to the proptosis, dilated facial veins, and depression of mental and physical activity has been unfavorable. The parents have considered the results worth while, because the patients were quieter and had fewer seizures.

COMMENT

Both in experimental studies and in studies on human beings it is apparent that there is no increase in the oxygen level in the superior sagittal sinus following a cervical carotid artery-internal jugular vein shunt. Depending upon the type of confluence of sinuses, it is conceivable that some oxygen may possibly get into the posterior portions of the superior sagittal sinus. Both in the rhesus monkey and in these limited experiences in human beings, the oxygen content in the sagittal sinus has been found to have decreased following the shunting procedure. No studies have been made of the actual uptake of oxygen by the tissues themselves. It may be desirable to study the oxidative processes of the cortex by determining the amount of lactic acid in the frozen live brain of the experimental animal following a cervical carotid artery-internal jugular vein shunt. If there is an increase in the lactic acid content of the brain under these circumstances, a relative anoxia may be concluded.

The changes in the electroencephalograms may be ascribed to various factors, including a relative anoxia of the tissues due to the stagnation of the venous blood in the sagittal sinus, anesthesia, maturation of the patient, and factors unknown. The changes are too variable to be used as criteria upon which to evaluate the procedure.

The sagittal-sinus blood pressure increases appreciably in the immediate post-shunt period. This pressure dropped to the preshunt level in Case D. S.

In the rhesus monkey, when the opposite lateral sinus was ligated, angiography revealed that the dye injected into the jugular vein entered the sagittal sinus and its tributaries. However, in this group of experiments it was found that the sagittal-sinus oxygen content was not increased. The visualization of the sagittal sinus and its tributaries was attributed to the fact that when injecting the dye with a 10-cc. syringe through an 18-gauge needle, pressures of 350 to 500 mm. of mercury are reached, a level which is many times the systolic pressure in animals or human beings. Under the circumstance of ordinary levels of blood pressure, the systolic pressure is not sufficient to force the blood into the sagittal sinus.

The pattern of the confluence of sinuses undoubtedly is important in determining the type of angiograms obtained. In certain anatomic studies,[6] it has been shown that the sagittal sinus becomes continuous with the right lateral sinus, with a small communication between the two lateral sinuses; in others, the superior

6. Gray, H.: Anatomy of the Human Body, edited by C. M. Goss, Ed. 25, Philadelphia, Lea & Febiger, 1948.

sagittal sinus becomes continuous with the left lateral sinus; in still others, there is a T-shaped channel with good communication between the two lateral sinuses and the sagittal sinus. In a limited number of venograms of human beings, these various types of confluence of sinuses have been noted. In many examples, the confiuence is an adequate communication between the two lateral, the superior sagittal, and the straight sinuses.

CONCLUSIONS

1. Gasometric studies of the sagittal sinus blood before and after cervical arteriovenous shunts reveal that the oxygen content of the sagittal sinus blood is not increased following the shunting procedure.

2. There appears to be a change in the electroencephalographic pattern following the shunting procedure. This change is variable and nonspecific.

3. Angiographic studies following cervical carotid artery-internal jugular vein anastomosis reveal results essentially similar to those obtained in the rhesus monkey. The blood goes up the jugular vein on the same side, into the lateral sinus, thence to the lateral sinus on the opposite side, and down the contralateral jugular vein into the neck. Many of the neck tributaries may also transport the blood from one side of the neck to the opposite side.

4. Choked discs and proptosis may result from increased blood flow through the lateral sinuses as well as through the venous sinuses at the base, which engorge the cavernous-sinus neighborhood, thus preventing the normal venous flow from the orbits.

COMPLICATIONS AND EFFECTS OBSERVED IN THIRTY-THREE PATIENTS WITH CERVICAL ARTERIOVENOUS FISTULAS

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THE CERVICAL arteriovenous fistula was first described by Beck, McKhann and Belnap [1] as a means of increasing the blood supply to the brain. We used their procedure in 33 cases of cerebral palsy and have followed the patients for approximately one and a half years. In this series we found that certain immediate and late complications occurred.

The immediate postoperative course of the average patient was smooth. However, complications peculiar to this type of surgery did occur. Several patients had a transient edema of the eyelids that disappeared without treatment. One patient suffered from a headache in the left parietal area at the site of previous brain surgery. The pain disappeared immediately when the fistula was occluded temporarily. Hoarseness, which was usually due to laryngeal irritation from the intratracheal tube, cleared up on steam inhalations before the patient left the hospital.

If the fistula was made too small, it closed off spontaneously within the first few days. This occurred in children who had an atrophic jugular vein due to brain atrophy or previous injury to the sinus system.

Signs of increased intracranial pressure developed immediately if the fistula was constructed too large. Adults complained of severe headache and vomiting and became comatose. These conditions were remedied by surgically reducing the fistula to its proper size or eliminating it entirely. Immediately after such a procedure the symptoms disappeared and the intracranial pressure returned to normal. This particular complication occurred in children who had a very small internal jugular vein at the time the fistula was made. It was evidenced in the children by bulging fontanelles, separation of suture lines, vomiting, and weight loss.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1951.

1. Beck, C. S.: Ann. Surg. **128**:854-864, 1949. Beck, C. S.; McKhann, C. F., and Belnap, W. D.: J. Pediat. **35**:317-329, 1949. McKhann, C. F.; Belnap, W. D., and Beck, C. S.: Cervical Arterio-Venous Anastomosis in the Treatment of Mental Retardation, Convulsive Disorders and Cerebral Palsy, Ann. Surg., to be published.

A number of patients complained of a buzzing sensation in the right ear. In order to avoid this complication, we constructed the fistulas between the common carotid artery and the internal jugular vein as low in the neck as possible. We did not have to close any fistulas to relieve this condition.

Atherosclerotic plaques were palpated in the carotid arteries of several of our adult patients. In one case a fistula was created at the site of an atherosclerotic plaque in a patient with severe essential hypertension. Several weeks after operation he bled from the wound and a seeping aneurysm was diagnosed. At operation a false aneurysm had formed at the distal end of the fistula. In this case the internal jugular vein was ligated, the aneurysm removed, and the defect in the artery wall repaired.

Several patients complained of an increase in neck size after the arteriovenous fistula. This increase in size was the result of aneurysmal dilatation in the right internal jugular vein.

After a cervical arteriovenous fistula was produced, the vein, being subjected to a greater pressure, hypertrophied and became tortuous. The thickening in the vein wall was due to fibrosis occurring in the adventitial area. No changes were noted in the muscular media or intima of the vein. It is a well established fact that veins

Increasing Number of Cases with Complications

		Total Cases	Number of Months						
			1	3	6	9	12	15	18
Total number of cases showing complications at time interval named	Adults.....	22	10	13	17	19	20	21	21
	Children.....	11	9	9	10	11	11	11	11

dilate under pressure, as in the case of varicose veins. But in the case of the cervical arteriovenous fistula, these collateral veins dilated rapidly and some shunted the blood back to the heart, thereby greatly increasing its work. To eliminate this, even the smallest muscular branches emptying into the internal jugular vein were ligated up to the base of the skull.

The emissary veins in the diploë increased in size after the establishment of an arteriovenous fistula and became noticeable if a craniotomy was done.

Intracranial shunts occur. The ones we encountered involved a shunt through the inferior petrosal and cavernous sinuses, with the ophthalmic veins producing a proptosis. Another shunt was from the right lateral sinus through the torcular Herophili to the left lateral sinus down the left internal jugular vein, producing an increasing load on the right heart. Autopsies on several patients whose angiograms showed this type of shunt revealed right cardiac dilatation. A third shunt was through the inferior sagittal sinus and the great veins of Galen, into the veins draining the middle of the brain. Because such shunts may produce serious complications, we adopted the routine of doing an angiogram in a retrograde manner through the right internal jugular vein prior to surgical intervention. If one of the shunts was demonstrated, an arteriovenous fistula was considered to be contraindicated.

The operative mortality was 6% in the adult group. The deaths occurred in the immediate postoperative period, but they were not due to technical errors in the

surgical procedure. One patient died from aspiration pneumonia and the other from heart failure. There were no deaths among the children in the immediate postoperative period.

The accompanying table shows the total number of cases broken down into 22 adults (cerebral palsy following a stroke) and 11 children (cerebral palsy following birth injury). As the table indicates, the number of patients showing improvement decreased progressively with time until at the end of 18 mo. only 1 of the 33 patients could be considered improved.

The commonest complications which appeared during the 18 mo. were intracranial shunts, which could be demonstrated angiographically and which were manifest clinically by signs of increased intracranial pressure (headache, nausea, vomiting, proptosis, dizziness, and scleral injection) and by changes in the Queckenstedt sign.

CONCLUSION

In a series of 33 cases in which a cervical arteriovenous fistula was done, only one patient showed improvement after 18 mo. Therefore, we believe that this procedure has little if anything to offer in the way of therapy for cerebral palsy from either birth injury or stroke.

SYNDROME OF THE LEAKING DUODENAL STUMP

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THE LEAKING duodenal stump following gastric resection presents a definite problem in gastric surgery. Though much has been said, and fittingly so, about the prevention of this complication, so far as we have been able to determine nothing has been said of early recognition of the lesion once it has occurred. The leaking duodenal stump causes characteristic symptoms and signs which permit an early diagnosis. The purpose of this paper is to describe the syndrome.

A review of the case records of 500 subtotal gastric resections revealed the incidence of proved disruption of the duodenal stump to be 3%, or a total of 15 cases. Duodenal stump disruption was proved at operation, or by the development of an external bile fistula, or at autopsy. Of the 15 patients, only two had their symptoms correctly diagnosed early, and only these two were operated on for the express purpose of relieving this complication. Both of the patients survived. Of the remaining 13 patients, 11 died and 2 survived, a mortality rate of 85% in patients for whom an early diagnosis was not made. In 10 of these patients, external bile fistulas developed spontaneously or followed the late drainage of obvious abscesses (Table).

The frequent failure to recognize the definite clinical entity of the leaking duodenal stump is surprising. The disastrous consequence of failure is evident. The reason for failure is confusion between pulmonary and intra-abdominal lesions, perhaps due to the fact that the marked frequency of pulmonary complications in the era prior to antibiotics and early ambulation conditioned surgeons to think first of pulmonary lesions. As a matter of fact, in this series of cases pulmonary lesions were commonly present along with the disrupted duodenal stump.

No characteristic symptoms or signs precede rupture of the duodenal stump. A certain restlessness and apprehensiveness and perhaps a feeling of fullness was described occasionally in the nurses' notes. Nausea, vomiting, unusual output of gastric drainage or other evidence of poor function was not found.

Duodenal stump disruption occurred on the second to the seventh postoperative day (Chart 1). The accident may result in dramatic changes in an otherwise normal postoperative course but may be obscure when leakage from the duodenal stump is minimal or if the accident occurs when the clinical picture is already complex because of other postoperative complications.

SYMPTOMS

Pain.—Pain at the time of disruption of the stump is the most constant subjective finding. The onset is usually sudden and may waken the patient at night. The pain is sharp, severe, constant, well localized to the right upper region of the

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abdomen and does not radiate. If the patient is receiving narcotics postoperatively, the sharpness of the pain is diminished and may be further obscured by the continued use of these drugs. As time goes on, it tends to lessen, and it spreads from the right upper quadrant toward the right lower quadrant, then toward the upper left quadrant, and finally over the entire abdomen. This process seems to take 24 to

Summary of Fifteen Proved Cases of Disrupted Duodenal Stump Following Gastric Resection

Case No.	Diagnosis	Estimated Day of Disruption	Postoperative Course	Major Autopsy Findings
179-499	Carcinoma of stomach	5	Bile fistula, 8th day; wound disruption, 8th day; died, 11th day	Disruption of stump; peritonitis with right subphrenic abscess
184-668	Duodenal ulcer	3	Bronchopneumonia; died, 7th day	Disruption of stump; peritonitis; bronchopneumonia
177-696	Duodenal ulcer	6	Bile fistula, 8th day; wound disruption, 9th day; thoracenteses for left empyema, 11th, 12th and 13th days; died, 14th day	Disruption of stump; peritonitis with pyloric, left subphrenic, and pelvic abscesses; fibrinopurulent pleuritis
188-145	Duodenal ulcer	5	Bile fistula following incision and drainage of subhepatic abscess, 9th day; died, 21st day	No autopsy
192-706	Carcinoma of stomach	7	Wound disruption, 8th day; bile fistula, 10th day; incision and drainage of subhepatic abscess, 12th day; died, 15th day	Disruption of stump; peritonitis; bronchopneumonia
196-650	Carcinoma of stomach	3	Wound abscess, 11th day; bile fistula, 16th day; fistula closed spontaneously, 28th day; discharged, 47th day	Survived
201-180	Hypertrophic pyloric stenosis	7	Gastrostomy, 7th day; bile fistula, 11th day; died, 14th day	Disruption of stump; peritonitis
203-913	Acute and chronic gastritis, severe	2	Bile fistula, 4th day; died, 18th day	Disruption of stump; disruption of gastrojejunostomy; peritonitis
154-630	Duodenal ulcer	6	Pneumoperitoneum, 6th day; bile fistula following incision and drainage of subphrenic abscess, 12th day; incision and drainage of subphrenic abscess, 28th day; discharged, 51st day	Survived
118-103	Duodenal ulcer	3	Died, 6th day	Disruption of stump; peritonitis
63063	Pyloric ulcer	4	Bile fistula, 15th day; died, 16th day	Disruption of stump; peritonitis with subhepatic abscess; bronchopneumonia
72726	Duodenal ulcer	2	Died, 7th day	Disruption of stump; peritonitis; focal fat necrosis
72846	Duodenal ulcer	4	Operation for leaking duodenal stump, 5th day; discharged, 25th day	Survived
292-675	Duodenal ulcer	6-8 (?)	Incision and drainage of subphrenic abscess, 11th day; bile fistula, 17th day; wound disruption, 19th day; died, 27th day	No autopsy
74169	Duodenal ulcer	3	Operation for leaking duodenal stump, 3d day; fistula closed spontaneously, 29th day; discharged, 39th day	Survived

48 hr. or longer but may never occur if a spontaneous external duodenal fistula develops. Shoulder pain is not characteristic (one or possibly two cases in 15). It has been noted that when the patient takes a deep breath the pain is increased, and this accounts for the shallow respirations usually seen. Peculiarly enough, one patient denied pain, though he did definitely admit tenderness.

Tenderness.—Tenderness in the right upper abdominal area is the most constant physical finding after disruption of the duodenal stump. As nearly as we could tell, it was present in all the cases reviewed. Certainly in the cases personally seen it was

definite and constantly present. A right upper abdominal incision may obscure the intra-abdominal tenderness, but in our experience careful examination with the dressings removed revealed this complaint to be definitely more marked and more widespread than that customarily found. Rebound tenderness was also present. Tenderness spreads along with the peritonitis, until the characteristic tenderness of generalized peritonitis is present.

Muscle Spasm.—This symptom, or at least voluntary muscle guarding, is an almost constant objective finding, and initially it is localized to the right upper abdominal quadrant. The boardlike abdomen so characteristic of a ruptured ulcer is not present. The muscle spasm or resistance will be found only if the dressings are removed and the patient carefully examined. It spreads along with the peritonitis, becoming generalized when the peritonitis is diffuse. It is important to note that early, when the diagnosis should be made if good results are to be hoped for,

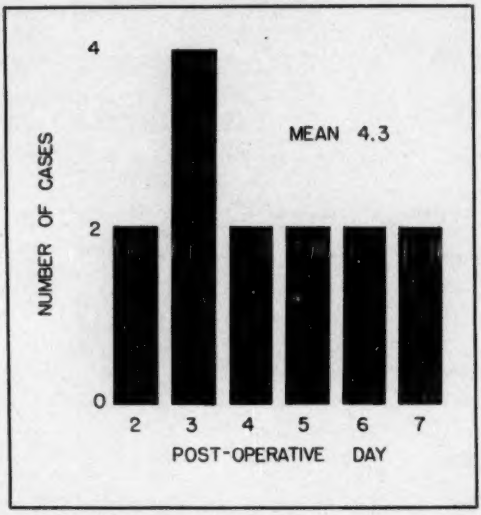

Chart 1.—Estimated day of disruption of duodenal stump. One case is not included because of inaccurate data.

pain, tenderness, and muscle spasm are well localized, probably because the quantity of leaking bile and pancreatic juice is not great and with it there is little or no irritating gastric juice and because the peritoneal reaction resulting from the preceding operation tends to wall off the process.

Distention is not present at the onset but develops with the spreading peritonitis. It was noted within 24 to 48 hr. in some cases, even though gastric suction was maintained.

Temperature.—Changes are characteristic. The temperature begins to rise immediately, or it may drop temporarily. After this initial variation, a definite, usually dramatic, and frequently marked rise occurs. As a rule the mean temperature rises progressively during the first 24 to 48 hr. A persistent high fever or a fluctuating type of septic fever then remains and is altered only by surgical intervention or by the development of a spontaneous fistula. The temperature changes

are not unlike those found with postoperative respiratory complications. Therefore, if signs are also present in the chest, the significant abdominal findings may easily be missed or disregarded, particularly if the administration of narcotics has not been discontinued.

Pulse Rate.—The changes are usually definite. The pulse rate rises at the onset and continues to rise as the peritonitis advances. The pulse may be thready if there is shock but returns to good volume until death is imminent. Initial shock is not characteristic. If there is an initial fall in blood pressure, it soon returns to normal. The extremities may be pale and cold, and even cyanosis has been noted, but these findings usually occur late, along with generalized peritonitis.

The white blood cell count is not helpful in attempting to establish an early diagnosis. Though it is usually increased, leukopenia was present in one-third of the cases in which determinations were made within 48 hr. Later the count rises in all cases.

Serum amylase determinations may or may not be of importance. They were not made in any of the cases reviewed. In one case, observed recently in consultation and not included in this series, no changes in the serum amylase were found on the second, fourth and sixth days after a minimal stump disruption had occurred. This patient was operated on six days after the leak began, and pancreatic enzymes and bile were recovered from the abdominal cavity. He survived. We have produced ruptured duodenal stumps experimentally in four dogs five days after subtotal gastric resection, without significant chages in the serum amylase levels. Perhaps this result was due to starvation.[1] Though it has not been proved, significant changes in the serum amylase may occur in some cases.

Chart 2 is a typical record in which postoperative disruption of the duodenal stump occurred in an otherwise uncomplicated case. The diagnosis was not made until a bile fistula developed on the eighth day. The patient died three days later.

The following are summaries of the two cases in which an early diagnosis was made and prompt therapy instituted. The patients survived.

Case 1 (Chart 3).—A white man, aged 49, underwent subtotal gastric resection for an extensive duodenal ulceration. On the fourth postoperative day, severe right upper abdominal pain occurred, with a sharp rise in the temperature and the pulse rate. He had a chill nine hours later, and the temperature rose to 40.9 C. (105 F.). He was thought to have a massive pulmonary collapse on the right, and the abdominal findings were said to have been minimal. The patient was seen in consultation (B. B. L.) 24 hr. after the onset of symptoms. The pain was less severe and localized in the right upper abdominal area. Tenderness and muscle spasm were limited to this region. An immediate exploratory operation was done. Bile, fat necrosis and severe fibropurulent peritonitis limited to the area of the disrupted stump were found. A soft tissue drain was inserted. The patient promptly improved. The duodenal fistula closed spontaneously in 21 days, and the patient has been symptom-free since.

Case 2.—A white man, aged 39, markedly obese, had severe duodenal ulceration which was intractable to medical therapy. Subtotal gastric resection was done, and bronchopneumonia followed. On the third day, severe right upper abdominal pain occurred. The temperature receded from 40.4 to 39.6 C. (104 to 103 F.), and then within 12 hr. rose to 41.4 C., (106 F.) with a pulse rate of 150 per minute, cyanosis and extreme mental confusion. There were right upper abdominal tenderness and muscle spasm extending to the left of the midline and down to the right anterior-superior spine. The left lower region of the abdomen was normal. Liver dulness was normal. Exploration 12 hr. after the onset revealed fibropurulent peritonitis, with

1. Pemberton, A. H.; Grindlay, J. W., and Bollman, J. L.: Serum Amylase Levels After Acute Perforations of the Duodenum: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **25**:5 (Jan.) 1950. Musgrove, J. E.: Elevated Serum Amylase Levels Associated with Perforated Gastroduodenal Lesions, Proc. Staff Meet., Mayo Clin. **25**:8 (Jan.) 1950.

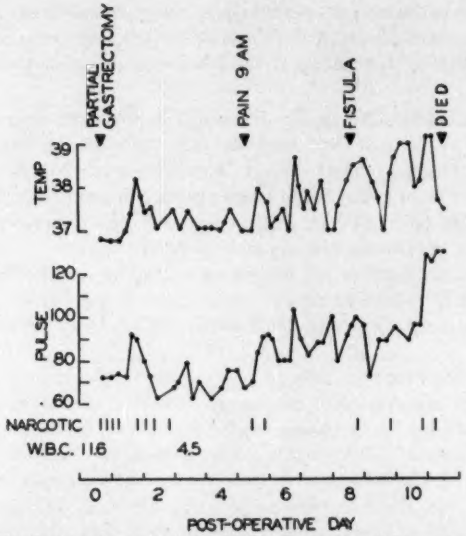

Chart 2.—Illustration of a normal postoperative course until disruption of the duodenal stump on fifth postoperative day, spontaneous external fistula three days later and death on the 11th postoperative day.

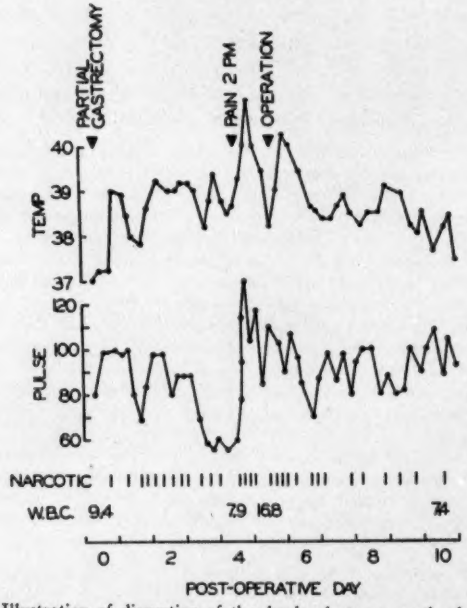

Chart 3.—Illustration of disruption of the duodenal stump on the fourth postoperative day followed by surgical drainage and recovery.

free bile and extensive fat necrosis about the disrupted stump. Repair was considered impossible. One rubber tissue drain was placed down to the stump. The patient's condition improved but remained critical because of the pulmonary complications and the copious duodenal drainage. The fistula closed spontaneously on the 29th day, and the patient has been symptom-free since.

CONCLUSIONS

Pain in the right upper region of the abdomen which is severe, constant, and nonradiating, associated with tenderness and moderate muscle spasm and accompanied with a progressive rise in the mean temperature and pulse, occurring most frequently three to six days after gastric resection, is the syndrome of the leaking duodenal stump (Chart 4). The initial symptoms and signs are usually confined to the right upper abdominal area because in all probability only a small amount of bile and pancreatic juice leaks from the stump early and little or no irritating gastric juice is present. The peritoneal reaction, due to the preceding operation, tends to

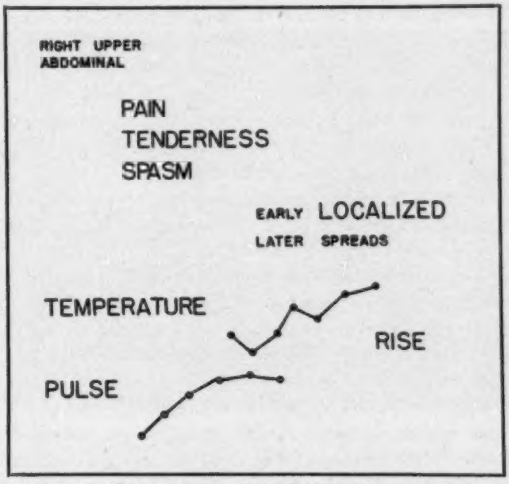

Chart 4.—The syndrome of the leaking duodenal stump.

keep the process localized. Even though the spread of peritonitis is relatively slow, generalized peritonitis does develop as a rule unless surgical drainage is instituted. A spontaneous external fistula or a walled-off abscess may occur.

Diagnosis of disruption of the duodenal stump is not difficult in a typical case if the possibility of its presence is borne in mind, if the abdomen is carefully examined with the dressings removed, if the use of narcotics has been discontinued, and if the clinical picture is not already complex because of postoperative pulmonary complications producing symptoms and signs which overshadow the less obvious abdominal findings. If the proper abdominal symptoms and signs are present, the diagnosis of a leaking duodenal stump should be made even though pulmonary complications are also present, because both may, and often do, occur together.

The prompt diagnosis of a leaking duodenal stump makes possible early surgical intervention when good results may be expected. There is reason to believe that failure to recognize the lesion, with consequent failure to intervene, will usually result in death.

PNEUMOARTHROGRAMS OF THE KNEE

An Aid in the Localization of Internal Derangement

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THE "TRICK knee" is familiar to every surgeon. Often he has only the patient's word for the time of the injury, the mechanism, the number of recurrences, the local reactions, and the like. In many instances, the symptoms and signs of internal derangement of the knee are minimal, intermittent, and evasive and the exact clinical diagnosis is by no means obvious. The decision as to whether the knee can stand the rigors of military service, athletics, or hazardous industrial occupations must be based on a questionable history and minimal findings on examination. Frequently the disturbance in such a knee is labeled "functional" because of the paucity of specific complaints and localized findings.

The temptation to solve the diagnostic dilemma by exploratory arthrotomy is always present; yet the knee is a joint that is not readily accessible to complete exploration. It is compartmented. There are medial, lateral, anterior, and posterior chambers, as well as a central space and superior pouch. The complete exploration of such a joint requires multiple incisions. An unnecessary arthrotomy is, of course, to be avoided, but one should particularly avoid the large or multiple exploratory incisions that are made necessary because of the inability of the surgeon to isolate the source of the trouble before operation.

We believe that air studies of the knee done under aseptic conditions and supervised by the surgeon or by an interested radiologist have a definite place in establishing accurately the diagnosis of internal derangement of this joint. Such a study is a definite aid in directing attention to the exact site of the pathologic process so that only the compartment involved may be entered, and it is particularly valuable in cases in which multiple lesions may be present in the knee.

TECHNIQUE

Pneumoarthrography of the knee has been performed since 1904, when Werndorff and Robinsohn [1] first reported its use. The technique has gradually advanced, the greatest contribution to it having been made in 1938, when Nordheim [2] used

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1951.

1. Werndorff, R., and Robinson, I.: Über intraarticulare und interstitielle Sauerstoffinsufflation zu radiologisch, diagnostischen und therapeutischen Zwecken, presented before the German Society for Orthopaedic Surgery, Fourth Congress, 1905.

2. Nordheim, Y.: Eine neue Methode, den Gelenkknorpel, besonders die Kniegelenkmenisken, röntgenologisch darzustellen (ohne Zuhilfenahme eingespritzten Kontrastmittels), Fortschr. Geb. Röntgenstrahlen **57**:479, 1938.

air in combination with spreading the joint. We have used routine pneumoarthrography for one and one-half years, with gratifying results.

Pneumoarthrography is done as an outpatient procedure. The knee is prepared surgically in the operating room and draped with towels. If there is fluid in the knee, the patient is placed on his abdomen so that the fluid will gravitate into the suprapatellar pouch and thereby facilitate its removal. If there is no fluid, the patient is placed on his back. This allows one to determine whether or not the air is entering the suprapatellar pouch.

A No. 25 gage needle is used for the installation of air. A small amount of 1% procaine hydrochloride is injected into the skin. The site of injection is the lateral superior pole of the patella, the depression at the lateral border of the vastus lateralis. Here the suprapatellar pouch may be entered with ease. When there is fluid, it is aspirated. The presence of fluid indicates that the needle is in the

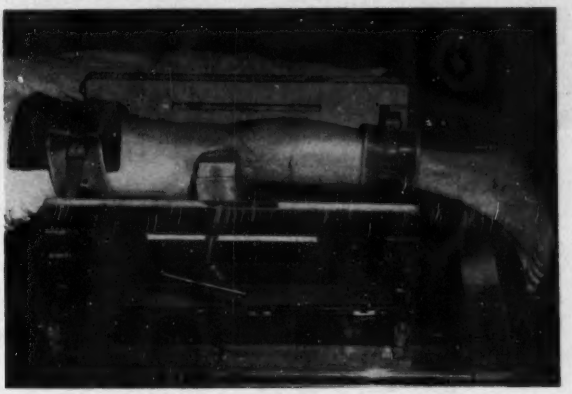

Fig. 1.—The patient is placed on his abdomen in the knee frame. The pusher is placed at the lateral side of the joint, and the medial side is spread. The pusher is changed to the opposite side for views of the lateral side.

suprapatellar pouch. When there is no fluid, air is injected and the filling out of the suprapatellar pouch is observed. There is a characteristic gurgle as the air enters the pouch. If there is no subcutaneous crepitation, the needle is in the suprapatellar pouch. A 30 cc. syringe and a three-way stopcock are used. Sixty to 90 cc. of operating-room air is injected. This is not enough to cause discomfort to the patient, who notes the sensation of the rising of his knee cap. The needle is withdrawn, and pressure is immediately applied to the site of the injection to prevent the escape of air into the subcutaneous tissues.

The joint line is then determined posteriorly by palpation of the tibial plateau. It is usually one-half inch (1.3 cm.) below the depressions in the popliteal fossa, lower than is expected. A transverse line is drawn on the skin as a guide for the x-ray. Pressure is applied to the suprapatellar pouch by means of an elastic bandage and the knee is flexed and extended, forcing the air into the recesses of the knee joint.

The patient is then placed face down on the x-ray table, with the knee in the special frame (Fig. 1). A soft-tissue technique is used, i. e., nonscreened cardboard cassettes, a 30 in. (76 cm.) distance, 80 kv., 100 ma., two-tenths of a second. A cone is used. The medial joint is spread, and a posteroanterior view is taken centered over the medial portion of the joint line. Oblique views are taken with the tube being shifted 20 degrees.

The same procedure is carried out over the lateral joint. The knee frame is removed, and the patient is turned on his affected side. A posterolateral view is taken. The cone is removed, and the tube is centered over the anterior part of the joint and elevated to 36 in. (91 cm.). This is done to include the suprapatellar

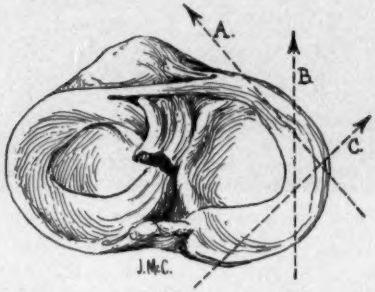

Fig. 2.—The normal medial meniscus. *A*, the anterior oblique projection. The wedge-shaped shadow is here one-fourth the width of the joint. The base is confluent with the capsule of the joint. The density is unchanged from the base to its knife-like point. The cartilage of the femoral condyle is unbroken from the thinner lateral portion to the thicker inner portion. *B*, the medial posteroanterior projection. The wedge is one-third the width of the joint space. The base is twice as thick and is confluent with the joint capsule, which is here the deep portion of the medial collateral ligament. The coronary ligaments are intact at both the superior and the inferior portion of the base of the meniscus. Air normally finds its way under the meniscus (thought to be by some authors a sign of pathologic changes). (Schum, H.: Dei röntgenologische Diagnostik der Meniskusverletzung, Röntgenpraxis **9**:369, 1937.) *C*, the normal posterior oblique medial meniscus. The wedge is one-half the width of the joint. The base of the meniscus is three times that of the anterior portion. The superior surface of the meniscus conforms to the curve of the femoral condyle. The inferior surface conforms to the flat surface of the tibial plateau. The base is firmly attached to the capsule. Here one may normally see a translucent area which represents the bursas between the base of the meniscus and the posterior portion of the medial collateral ligament and the coronary ligaments. The cartilage of the tibial plateau is of uniform density. This is one of the most important views, as the site of the tear is common. The inferior surface is particularly important.

pouch. The roentgenograms are seen wet. If they are not exactly centered or properly exposed, they are repeated. A poor roentgenogram is worthless. When the surgeon is satisfied with the view, air is removed by inserting a 20 gage needle in the same site of injection. The air is not completely removed and will remain for several days. If an arthrotomy is done on the second or third day, there will be

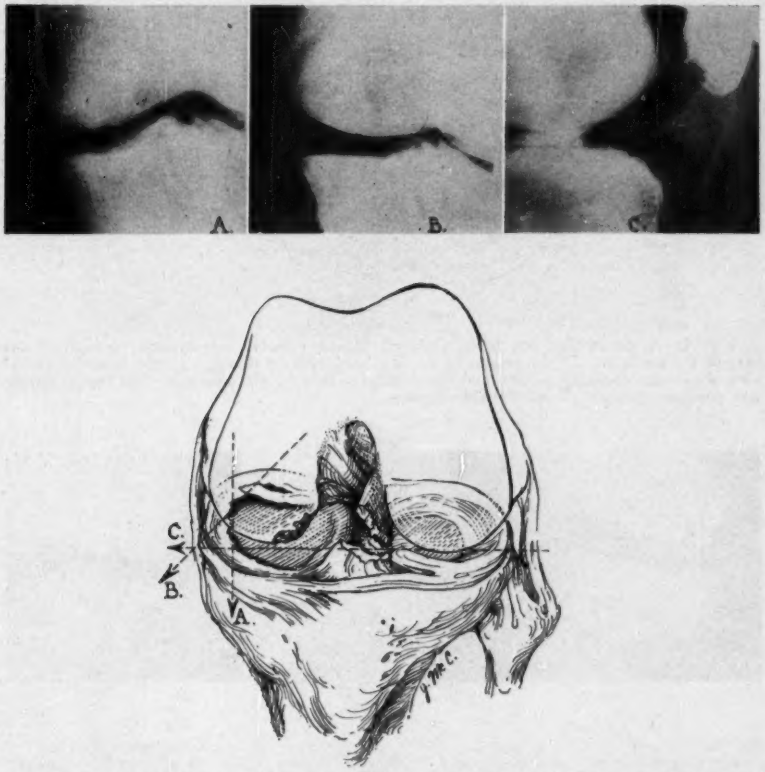

Fig. 3.—*A*, the wedge is absent on the roentgenogram. The drawing shows the remaining rim found at operation. *B*, the wedge is absent, and there is a superior displacement of the torn portion. There is also a break in the cartilage of the femur. The drawing demonstrates the defect seen. *C*, there is absence of a normal density in the anterior compartment of the knee. This represents a tear of the anterior cruciate ligament. An incision was used that allowed exploration of the anterior and posterior portions of the medial joint. The remaining portion of the meniscus was removed. The cartilage was shaved with a knife. No repair of the anterior cruciate ligament was attempted.

cloudy fluid. This is, however, sterile and shows marked eosinophilia, described first by Murray.[3] On the fifth day, the fluid is normal. In over 200 pneumo-

3. Murray, R. C., and Forrai, E.: Transitory Eosinophilia Localized in the Knee Joint After Pneumarthrography, B. J. Bone & Joint Surg. **32-B** (No. 1):74, 1950.

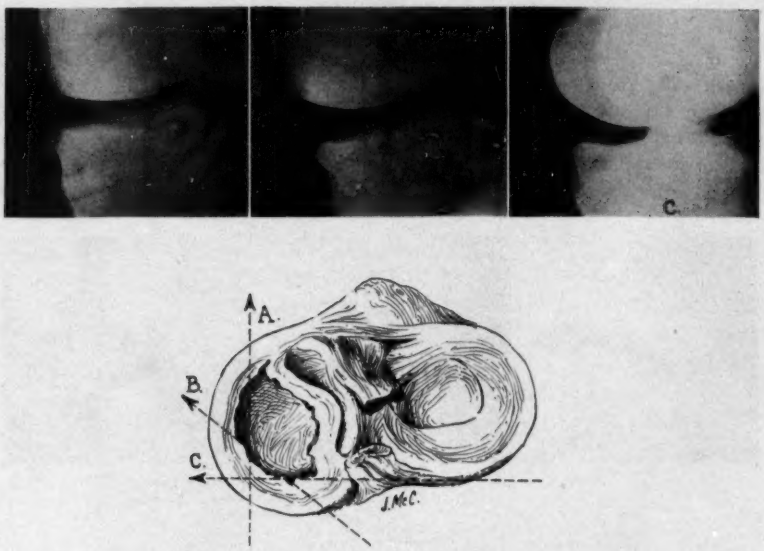

Fig. 4.—*A*, the wedge has been displaced. There remains but a small remnant of the base of the meniscus. *B*, the remaining portion is of uniform density. *C*, the posterior lateral view shows the displaced portion and the remaining base of the meniscus. The bucket handle was removed through a small anterior incision.

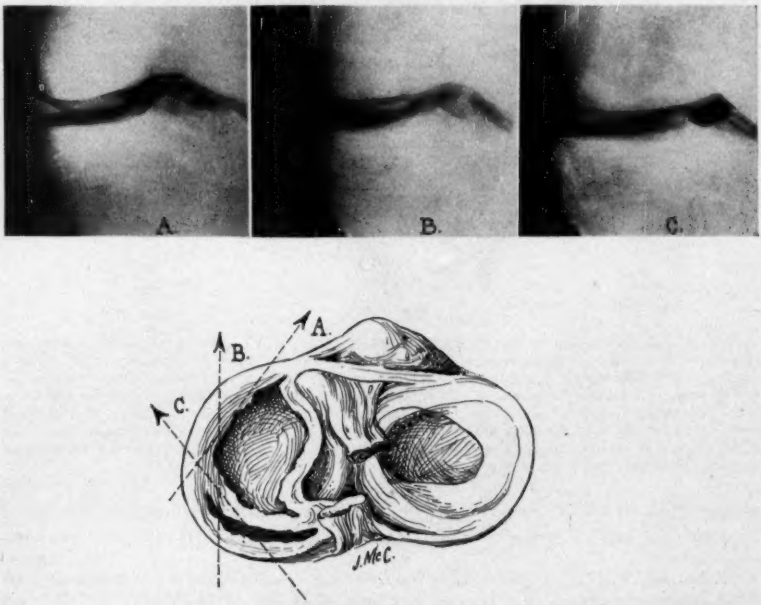

Fig. 5.—*A*, the anterior portion of the wedge. The apex is dense and blunt. There are densities in the joint, evidence of the displaced tear. *B*, the wedge does not end in the knife-like edge. The density is again seen in the joint space. *C*, in the posterior third of the meniscus, the base is irregular. The apex also shows density and blunting. An exposure was made which allowed the complete removal of the meniscus.

arthrograms, we have had no complications. A review of the literature indicates that air embolism is rare. One nonfatal case was reported in which this complication was due to the direct injection of air into a vein. Septic arthritis is another complication, and one case has been reported in the literature (Murray).

Interpretation of the roentgenogram must be made by the surgeon or by an interested radiologist. The surgeon has the benefit of the clinical history and examination. Also, he is more familiar with the pathologic process of internal derangement.

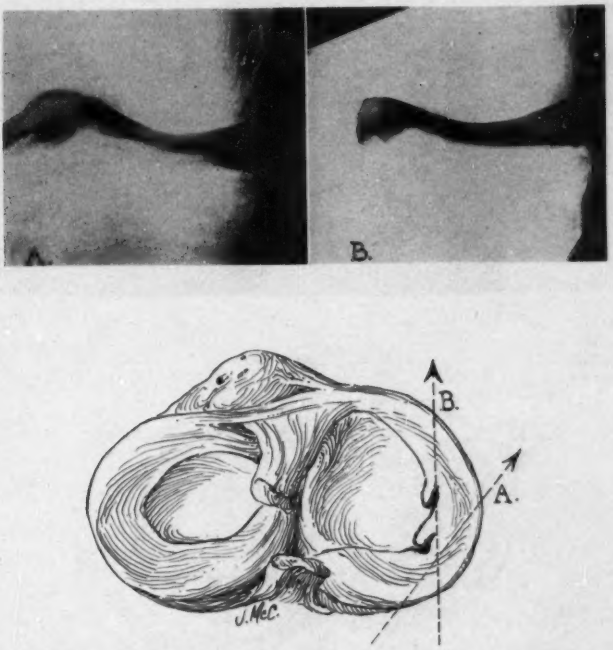

Fig. 6.—*A*, the knife-like edge is disrupted. There is a density which is not confluent with the edge of the meniscus. *B*, the posterior view shows a similar defect. There is no defect in the base of the meniscus. The two comma tears were found. The remainder of the meniscus was normal.

SUMMARY OF CASES

CASE 1.—*Multiple lesions* (Fig. 3).—G. M., a brakeman, had a history of an old injury to his knee and a recent injury to the same knee, resulting in pain, instability, and swelling which had failed to respond to conservative treatment. There was quadriceps atrophy, with a minimal amount of excess synovial fluid and no tenderness about the joint. There was a complete range of motion. The knee was stable on examination; however, the patient was able to force his femur posteriorly on the tibia.

CASE 2.—*Bucket-handle tear of the medial meniscus with displacement* (Fig. 4).—W. S. injured his knee while playing rugby two years prior to his recent injury, which was a flexing

twisting type resulting in his inability to extend the knee beyond 150 degrees. Physical examination showed quadriceps atrophy, an excess amount of synovial fluid, and tenderness over the anterior medial joint. The clinical diagnosis was displaced bucket-handle tear of the medial meniscus.

CASE 3.—*Multiple tears in the medial meniscus* (Fig. 5).—B. B. had received several injuries to his knee previous to the time of his complaint of instability, pain, and swelling. There were minimal atrophy of the vastus medialis, with no excess fluid, and tenderness over the anterior medial joint. There was complete range of motion, with no instability.

CASE 4.—*Comma tears at the inner margin of the meniscus* (Fig. 6).—J. F. complained of "something in his knee." He denied having received any injury, and there were no clinical abnormalities.

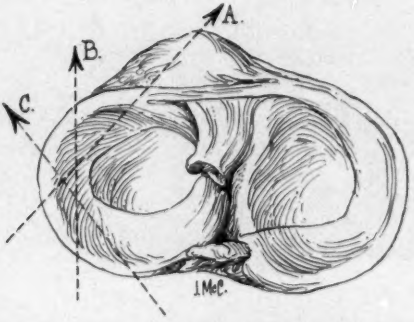

Fig. 7.—*A*, the wedge occupies one-third of the joint space. The inferior surface is displaced from the tibial plateau. There is a redundancy of the synovium. The density of the wedge is uniform from the lateral margin to the termination of the knife-like edge. The superior surface conforms to the femoral condyle. One may not pay attention to the defects seen in the base of the lateral meniscus, as the base is not closely adherent to the capsule. *B*, the medial view has nearly the same dimensions as does the anterior. The base may be much thicker than the one seen here. *C*, the posterior projection is the one in which the bursas of the popliteal tendon is seen. In this projection, the bursa is seen on the femoral condyle. The density of the popliteal tendon may be observed as it crosses the articular cartilage of the tibial plateau.

CASE 5.—*Normal lateral meniscus* (Fig. 7).—The roentgenogram in this case is more difficult to interpret because of overlying shadows and loose connection of the base to the joint capsule.

CASE 6.—*Tear of the lateral meniscus* (Fig. 8).—R. G. came into the Passavant Memorial Hospital because of a knee which would not extend beyond 150 degrees. There were pain and tenderness of the lateral side of the joint. The knee was manipulated without anesthesia and "unlocked." Two days later, a pneumoarthrogram was made.

These cases are presented to demonstrate the normal medial and lateral menisci as seen on pneumoarthrography and to show the application of pneumoarthrography to the diagnosis of the pathologic process involved in internal derangement of the knee. The cases illustrate the value of this method in establishing the diagnosis in questionable cases. It offers definite evidence on which the surgeon may establish criteria for an arthrotomy. In the obvious case, it is of value in demonstrating preoperatively whether the lesion is single or multiple. This acts as an aid in the planning of an adequate surgical approach and treatment.

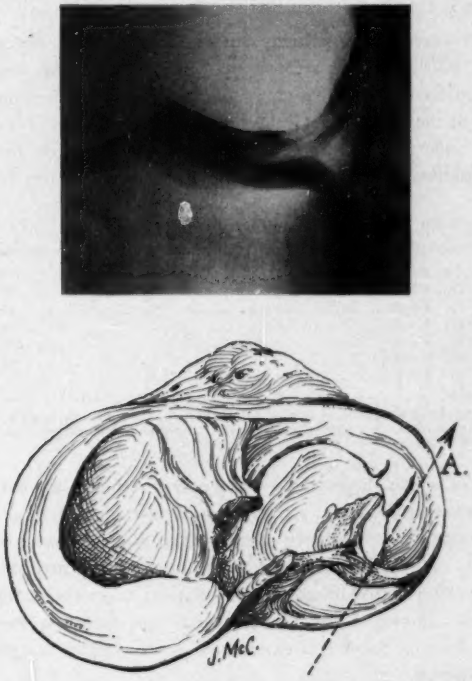

Fig. 8.—There were two defects in the wedge and a density in the joint medial to the wedge. This proved to be an avulsion of the posterior pole of the lateral meniscus with the ligaments of Humphrey and Wrisburg.

The cases also show the value of pneumoarthrography as the only means of obtaining objective evidence in cases in which there is a history of instability of the knee but no clinical abnormalities. They demonstrate its value in differentiating ligamentous tears and tears of the menisci. They show that pneumoarthrography has proved to be of value to the surgeon in determining the nature of the first injury and in directing the specific treatment.

Although it is impracticable to present here the roentgenograms and histories of all the cases in which we have used pneumoarthrograms to advantage, we have

found them to be helpful in establishing diagnoses in cases of discoid menisci and associated tears, hypertrophy of the fat pad, synovial tumors and other soft-tissue tumors about the knee. We have also found them helpful in examining the knee postoperatively for remaining tears or adhesions, determining the regeneration of the meniscus, demonstrating the connection of Baker's cysts with the knee joint, demonstrating the defect of the articular cartilage over the area of osteochondritis dissecans, and determining the position of a free body (chondral fracture), whether it is inside or outside the synovial cavity.

ANALYSIS OF RESULTS OF PNEUMOARTHROGRAPHY

The table represents 144 patients studied by means of pneumoarthrography. Of this number, 107 underwent arthrotomy. In 75 of these the diagnosis was made from a combination of clinical and pneumoarthrographic findings. The lesions were confirmed at the time of surgical intervention. Nineteen of the patients in this group did not undergo arthrotomy either because they were for one reason or another not considered to be good surgical risks or because they refused operation.

*Data on 144 Cases**

C+ P+ S+	75
C+ P+ So	19
C+ P+ S−	2
C+ P− S−	2
C− P+ S−	1
C− P+ S+	27
C− P− So	18

* C+ denotes arthrotomy indicated by clinical criteria; P+, defect demonstrated by pneumoarthrogram; S+, lesion proved at operation; C−, questionable case; P−, normal pneumoarthrogram; S−, no lesion found at operation, and So, no operation.

In 27 cases in which there was a history of instability but not enough clinical evidence to warrant an arthrotomy, the pneumoarthrogram acted as a positive aid in establishing the diagnosis. Eighteen pneumoarthrograms gave no evidence of internal derangement. We considered these cases unsuitable for arthrotomy. However, a long enough period of follow-up has not elapsed to establish the correctness of these conclusions. In two of the cases in this group, operation was performed and no lesions were found. After this experience, more weight was given to pneumoarthrographic findings.

We did have some failures. Two were the result of misinterpretation through inexperience and acceptance of poor pneumoarthrograms. No lesions were found in the menisci. In one case, a shadow was misinterpreted as a tear of the meniscus with displacement. It proved to be hypertrophy of the fat pad.

While the 37 cases in which no operation was performed cannot be included in the statistics because the conclusions cannot be proved without arthrotomy, we feel that pneumoarthrography has been of use in these cases. It has been of value in a negative sense as well, although in only two cases was this proved by arthrotomy.

Our percentage of error was 4.7. We feel that the combination of clinical and pneumoarthrographic examination is of real value in establishing the diagnosis of internal derangement of the knee.

CONCLUSIONS

1. There is a need for a diagnostic aid in determining internal derangement of the knee joint.

2. The technique must be carried out carefully and aseptically. The roentgenograms obtained must be satisfactory in respect to direction of the x-ray and the density.

3. The surgeon must interpret the roentgenograms and correlate them with the clinical picture.

4. The procedure has value in the obvious case in directing the incision and treatment.

5. In the difficult case, the procedure is of value as a diagnostic aid in establishing the diagnosis and indications for arthrotomy.

6. There are no common complications from the careful use of pneumoarthrography with the exception of eosinophilia.

7. The procedure has been useful in giving negative as well as positive diagnostic evidence.

CONSIDERATION OF THE LETHAL FACTORS IN ACUTE PANCREATITIS

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CINCINNATI

IN THE 10-year period 1941-1950 inclusive, there were 164 cases of admission for acute pancreatitis to the Cincinnati General Hospital. In each case the diagnosis was based on at least one of the following criteria: (1) a consistent clinical history in conjunction with increased serum amylase; (2) surgical observation, and (3) post-mortem examination. In each case acute pancreatitis was the major factor in the illness.

The disease acute pancreatitis falls into three general clinicopathological subtypes, as indicated in a previous report:[1] 1. Acute interstitial (edematous) pancreatitis, usually self-limiting and rarely fatal, is identified at operation or at necropsy by induration and swelling of the pancreas without softening or hemorrhage. In the absence of anatomical verification, a patient with acute pancreatitis is arbitrarily placed in this group if the clinical course is benign and if there is no evidence of hemorrhage, necrosis, or suppuration in and about the pancreas. One hundred and thirty cases of the present series have fallen into this classification. 2. Acute pancreatitis with hemorrhage and necrosis, proved at operation or necropsy, was found in 15 cases of this series. 3. Acute pancreatitis with suppuration or pseudocyst, characterized by the presence of an intra-abdominal mass, occurred in 18 cases of the series. The mortality within the entire group of 164 cases was 14.0%, in contrast to the previously reported mortality rate of 18.0% for the years 1941 to 1948 inclusive[1] (Table 1). It is significant that during the past two years the mortality rate for acute pancreatitis in this hospital reached an unusually low figure, 5.7%.

Despite the encouraging fall in mortality rate when a comparison is made with previous reports,[2] the cause and mechanism of death in fatal cases of acute pancreatitis are generally not understood and the clinical features of the lethal form of the disease are not established. An extensive analysis of the clinical features of acute pancreatitis observed in this hospital has been made elsewhere.[1] Rather than dwell on the successful results of this series, we propose to examine the failures by

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Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1951.

From the Department of Surgery, University of Cincinnati College of Medicine, and the Cincinnati General Hospital.

1. Siler, V. E., and Wulsin, J. H.: Acute Pancreatitis, J. A. M. A. **142**:78 (Jan. 14) 1950.

2. Morton, J.: Acute Pancreatitis, Surgery **17**:475, 1945. Schmieden, V., and Sebening, W.: Surgery of the Pancreas, Surg., Gynec. & Obst. **46**:735, 1928.

analyzing the records of those patients who succumbed to acute pancreatitis. A group of 22 fatal cases, in each of which operation or postmortem examination was carried out, has been studied. Necropsy was performed in 91% of these cases.

AGE

Two-thirds of the fatal cases involved patients who were 51 yr. or older, an incidence which suggests that diseases of advancing age, especially those of the cardiovascular system, may play an unrecognized role in fatal pancreatitis.

SEX

Among the patients who died were 14 women (63%), a sex incidence similar to that of the entire series. There was no difference in racial incidence between fatal and nonfatal cases; in both groups white patients accounted for approximately 60% of admissions for acute pancreatitis (Table 2).

TABLE 1.—*Clinicopathological Classification and Mortality Rate*

Clinicopathological Type	Number	Fatal Cases	Mortality, %
Hemorrhagic	15	12	80.0
Suppurative (pseudocyst)	18	6	33.3
Interstitial	130	4	3.1
Unclassified	1	1	100.0
Total	164	23	14.0

TABLE 2.—*Age, Sex and Race Distribution in Twenty-Two Cases of Lethal Acute Pancreatitis*

Years	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Cases	0	1	2	3	2	5	6	3

Sex	No. of Cases	%	Race	No. of Cases	%
Female	14	63	White	13	59
Male	8	37	Negro	9	41

CLINICAL HISTORY

Although not characteristic enough to afford an accurate prognosis, the clinical history in the fatal cases generally indicated a more severe symptomatology than that in benign cases. Two patients arrived at the hospital in terminal coma. Eighteen of the remainder noted an onset of illness with abdominal pain, usually severe, although this symptom developed in all cases sometime in the course of the illness. The pain was predominantly in the upper part of the abdomen but occasionally was generalized, and at times it was prominent in the lower part when extensive retroperitoneal spread of the inflammation had already occurred. Although in two cases the duration of illness prior to admission was only three hours, 13 patients were seriously ill for at least a day before reaching the hospital. This fact suggests that earlier treatment might have aided in preventing a fatal outcome. Two patients had previously been treated in this hospital for known attacks of acute pancreatitis of the interstitial variety. Most of the patients had experienced previous epigastric distress or pain over a period varying from a few weeks to many years.

The most striking feature discovered on physical examination in the fatal cases was the presence of peripheral circulatory collapse in 10 of the 22, evidenced by clammy, pale or cyanotic skin, weak, rapid pulse, and low or absent blood pressure. In seven cases there was temporary response to intravenous administration of blood and fluids even though the blood pressure when first taken was absent, but in three instances the peripheral circulatory collapse was irreversible. When first seen, only one-third of the patients who died had a temperature of 100 F. or more, but terminally pyrexia was a common and ominous sign. Four cases showed jaundice on admission to the hospital or later during their course. The cause of the jaundice was an inflamed head of the pancreas in two instances, a common duct

TABLE 3.—*Clinical Features*

Feature	No. of Cases	%
Duration before admission		
12 hr. or less	6	27
12 hr. or more	14	63
Abdominal pain	20	91
Temperature on admission		
100 F. or higher	7	32
Below 100 F.	15	68
Peripheral circulatory collapse	15	68
Jaundice	4	18
Abdominal tenderness	19	86
Upper abdominal mass	7	32

TABLE 4.—*Laboratory Data*

Test		No. of Cases	%
White blood cells, 10,000 plus		15	68
Albuminuria		13	59
Blood serum amylase	increased	10	45
	normal	3	14
	not determined	9	41

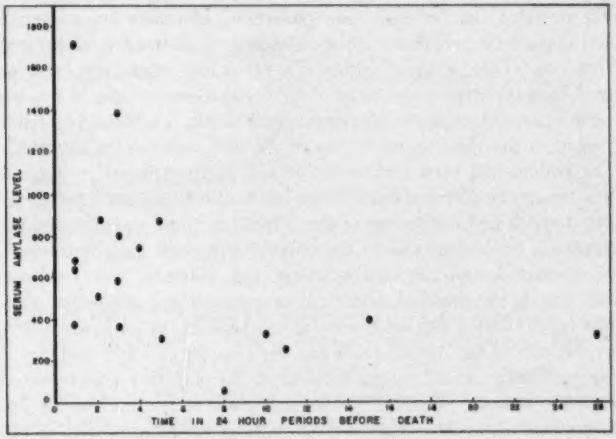
stone in one instance, and acute cholecystitis with questionable hepatitis in the other. In the admitting room all patients, with the exception of two in a terminal condition and one with massive hematemesis, presented abdominal tenderness, most commonly generalized and usually maximal in the upper quadrant, corresponding to the location of the most severe pancreatic damage. Lesions in the head of the pancreas caused right-sided tenderness and those in the tail, left-sided tenderness. Seven cases presented a palpable upper abdominal mass, which in two instances represented fat necrosis in the omentum (Table 3).

Routine laboratory tests presented nonspecific results. In two-thirds of the fatal cases the white blood cell count amounted to 10,000 or more cells per cubic millimeter. On urinalysis, in 13 of 19 cases tests showed albuminuria not accounted for by cellular sediment. This finding is perhaps a reflection of the toxic effects of the disease on the kidneys (Table 4).

SERUM AMYLASE

In the absence of laboratory or necropsy findings, acute pancreatitis can be accurately diagnosed with knowledge of the clinical course and with the finding of increased serum amylase, as repeatedly stressed by many authors.[3] Despite the easy availability of the serum amylase test in this hospital,[4] it was startling to find that in nine of the 22 fatal cases no serum amylase determination had been made and that in three others only one determination, reported as normal in each instance, was made. Unfortunately in these 12 cases a proper diagnosis was not reached prior to operation or postmortem examination (Table 4).

An increased serum amylase level was found in 10 fatal cases prior to operation or necropsy. In general, the serum amylase value was moderately high rather than extremely so, and occasionally it was only slightly increased (chart). Contrary to expectation, markedly increased values (above 2,000 units) did not indicate



Dot diagram showing distribution of the serum amylase values in nine patients who succumbed to acute pancreatitis.

a fatal prognosis, and in a number of patients with high values on admission the disease pursued an entirely benign course, as seen in the interstitial type. When the pancreas is extensively damaged, the amylase may fall to normal or subnormal values. A likely explanation is that the diffuse destructive process stops the formation of amylase. In the fatal cases the serum amylase remained increased instead of falling within a day or two as in the benign cases. The average value for the serum amylase test in nine fatal cases was relatively low, 593 units.

An incorrect diagnosis, preoperative and antemortem, was made in 14 of the 22 fatal cases. This is a discouragingly high incidence and must be a significant factor in the fatal outcome for these patients. Proper use and evaluation of the serum

3. Elman, R.: Surgical Aspects of Acute Pancreatitis, J. A. M. A. **118**:1265 (April 11) 1942. Paxton, J. R., and Payne, J. H.: Acute Pancreatitis, Surg., Gynec. & Obst. **86**:69, 1948.

4. The serum amylase was determined by a modified Somogyi method, which yields normal values up to 200 units.

amylase test would have increased diagnostic accuracy and would have prevented fatalities. An analysis of the incorrect diagnoses may help to lower fatality rates in the future.

Three patients for whom a false diagnosis of acute cholecystitis was made were found at operation to have acute pancreatitis which in the postoperative period failed to respond to surgical drainage. Two other patients were thought to have acute perforated appendicitis. In one of these patients, a 40-yr.-old male Negro, appendectomy was performed on admission, and four days later laparotomy for a supposed bowel obstruction was done. At neither operation was the preoperative diagnosis sustained, and the proper diagnosis of hemorrhagic pancreatitis was not made until necropsy 10 days after the patient's admission. A serum amylase determination would have spared this patient useless operations and probably have saved his life. Two other patients entered the hospital with massive gastrointestinal bleeding and died shortly after being treated for bleeding peptic ulcer. Postmortem examination revealed that in each case pancreatic abscesses lay adjacent to the stomach and duodenum and that multiple bleeding ulcerations were present in the duodenal mucosa. One of these patients, a 60-yr.-old white man and a known alcoholic, had been admitted to the surgical service twice within the 15 mo. preceding death because of attacks of acute interstitial pancreatitis. A transitory tender mass had been found in the right upper region of the abdomen over a period of several weeks. The patient had been uncooperative and had continued to overindulge in alcohol, even though he suffered from severe intermittent epigastric pain. A barium study of the stomach and duodenum in the outpatient clinic had revealed no abnormalities. After his final admission to the hospital with fatal gastrointestinal hemorrhage, one normal serum amylase reaction was obtained and was considered insignificant, despite the previous history of pancreatitis and abdominal pain. Necropsy in this case revealed that an abscess at the head of the pancreas had ruptured into the second part of the duodenum below the ampulla of Vater and that the fatal hemorrhage had been caused by an erosion of the superior pancreaticoduodenal artery within the abscess. Careful histological study of the wall of the duodenum adjacent to the pancreatic abscess showed no evidence of peptic activity and indicated that the duodenal ulceration was secondary to an expanding pancreatic abscess. This fatality might have been prevented by more careful follow-up and by more stringent attention to the patient's dietary habits in view of two known attacks of acute pancreatitis.

CLINICAL COURSE

The clinical course in the hospital of the patients who died varied in duration. Eleven patients (50%) died within two days of their admission. Six more died within 10 days, and the remainder survived for several weeks. The majority of the patients succumbed promptly to the disease, some within several hours.

The presence of peripheral circulatory collapse either on the patients' admission or during the hospital stay was a serious and ominous prognostic sign, noted in 15 of the 22 fatal cases. On the other hand, it rarely appeared during the course of nonfatal cases of acute pancreatitis. Although vigorous intravenous therapy with blood, plasma, and isotonic solutions often temporarily restored adequate circulation, the subsequent clinical course was all too frequently one of sudden, recurrent peripheral circulatory collapse in association with terminal pyrexia. Thirteen

patients in the series died in this manner. The cause of the circulatory collapse was not obvious and could not always be accounted for by loss of blood into the peritoneal cavity and the retroperitoneal structures. One patient in severe terminal collapse was maintained satisfactorily with intra-arterial transfusion for several hours; yet necropsy revealed no intra-abdominal hemorrhage. In several instances, immediately prior to terminal collapse the patients appeared to be progressing satisfactorily and gave no warning of impending disaster. Occasionally circulatory collapse was so sudden and profound as to suggest the false diagnosis of severe coronary occlusion. The presence of shock in acute pancreatitis must always be considered a warning of grave danger.

Not all patients succumbed in a state of circulatory collapse. Nine of this group had a gradual downhill course marked by fever and terminated by sepsis and asthenia. Those patients with uncontrolled pancreatic and retroperitoneal abscesses presented tender abdominal masses and signs of generalized toxicity (Table 5).

TABLE 5.—*Clinical Course*

		No. of Cases	%
Survival after admission	48 hr. or less	11	50
	3-10 days	6	27
	11 days plus	5	23
Gastrointestinal hemorrhage		10	45
Fatal peripheral circulatory collapse		13	59
Terminal febrile course		9	41

CAUSE OF DEATH

The cause of death in acute pancreatitis could not be attributed to any single factor common to all cases. In certain instances death might have been prevented by appropriate measures prior to or at the time of the fatal illness, but in others the fatal progress of the disease defied all therapy. Postmortem examination was performed in 20 of the 22 fatalities. This remarkably high incidence resulted in part from the large proportion of fatal cases (12 patients, 55%) not correctly diagnosed prior to necropsy. If postmortem examination were carried out in more undiagnosed fatal cases, the incidence of fatal pancreatitis would probably rise and the disease would offer an increased challenge to the clinician. The fact that less than half of the fatalities occurred among cases properly diagnosed and treated as acute pancreatitis might be considered as an encouraging sign of more effective therapy, but it is also convincing proof of the urgent need for establishing a correct clinical diagnosis.

Four fatal cases were classed as acute interstitial pancreatitis. Two of the patients involved died suddenly several hours after reaching the hospital. At necropsy in both instances, pale, firm swelling of the pancreas was present and extensive fat necrosis throughout the peritoneal surfaces was found. In one of these patients, an 18-yr.-old male Negro, fat necrosis and bloody fluid were found in both pleural cavities as well as in the abdomen. The cause of death in such instances could not be explained by the extent of anatomical damage but must have been caused in part by profound chemical changes in the blood stream and the interstitial fluids.

Six fatal cases were diagnosed at necropsy as suppurative (pseudocystic) pancreatitis. In such cases, correct clinical diagnosis affords the best chance of recovery, since this form is amenable to surgical drainage, often in conjunction with antibiotic therapy. In two instances an uncontrolled pancreatic abscess extended retroperitoneally into the lumbar gutter and caused massive generalized peritonitis after rupture into the peritoneal cavity in one case and induced gangrene of the left colon in the other. Fatal gastrointestinal hemorrhage from ulceration of the stomach and the duodenum, as already mentioned, occurred in association with abscesses of the pancreas in two patients. Proper care of the abscesses prior to the stage of gastrointestinal ulceration might have prevented a fatal outcome. Another patient died with pulmonary infarction secondary to an abscess in the head of the pancreas, with thrombosis in the veins neighboring the abscess. The other patient died of intractable diabetes after drainage of an extensive pancreatic abscess.

Twelve fatal cases were classed as acute hemorrhagic pancreatitis with necrosis. Nine of the patients died in peripheral circulatory collapse, while three pursued a febrile, septic course. In two instances of circulatory collapse, death was attributable to secondary perforation and gangrene of the transverse colon caused by the primary peripancreatic necrosis. In the majority of these cases, however, the gross anatom-

TABLE 6.—*Cause of Death in Twenty Necropsies*

Clinicopathological Type	No. of Cases	%	Comment
Hemorrhagic	12	55	9 Peripheral circulatory collapse 3 Delayed febrile course
Suppurative	6	27	2 Massive gastrointestinal hemorrhage 2 Large retroperitoneal abscess 1 Pulmonary infarct 1 Intractable diabetes
Interstitial	4	18	3 Peripheral circulatory collapse 1 Protracted sepsis

ical findings at necropsy did not explain the cause of death, even though they established the diagnosis. In several instances the pancreatic necrosis and hemorrhage were limited to the head, body, or tail. A more striking and perhaps significant finding was the presence of edema and hemorrhage in the peripancreatic tissues, such as the fatty mesenteries, the periadrenal fat, and the periaortic tissues covering the autonomic nerves and ganglions (Table 6).

The association of gallbladder disease and pancreatitis has long been noted, although the significance of this association is not established. Cholelithiasis was present in 10 cases, with associated choledocholithiasis in four of these. In another patient choledocholithiasis alone was found. In no patient was a stone found impacted in the ampulla of Vater. In several cases of common duct stone, the pancreas showed evidence of necrosis and hemorrhage in either the body or the tail but not in the head of the gland. Ulceration of the stomach and duodenum was found in three cases. The incidence of these complicating conditions did not exceed that found in the entire series of fatal and nonfatal cases of acute pancreatitis. Operation was performed in seven of the fatal cases. In two instances successful drainage of a pancreatic abscess was obtained, although pulmonary embolus in one case and intractable diabetes in the other were responsible for death. In the remaining five cases, operation consisted of abdominal exploration, with drainage of the

pancreas or the lesser peritoneal sac. All five patients did poorly postoperatively and appeared to suffer from the procedure; in none of the five was a correct diagnosis made preoperatively.

COMMENT

The encouraging drop in the mortality rate of acute pancreatitis in this clinic during the past two years results, we believe, from two factors, namely, (1) an increasing ability to diagnose nonfatal acute pancreatitis with the help of more widespread use of the serum amylase test, and (2) a regimen of conservative, supportive therapy. Operation in the acute stage is reserved for patients given a diagnosis of abscess in the pancreas or adjoining abdominal structures. In cases of acute pancreatitis in association with proved gallbladder disease, operation generally should be deferred until the clinical symptoms and the serum amylase test indicate abatement of the acute phase of pancreatic inflammation. We believe that this policy has lowered the incidence of pancreatic complications (abscess and hemorrhagic necrosis) and has helped to prevent fatalities from acute pancreatitis.

When the diagnosis of acute pancreatitis is proved, the course and outcome cannot be prognosticated with certainty. From a study of the clinical features of these fatal cases, it is not possible to state definitely which patient will survive. Certain clinical observations, however, will be of assistance in alerting the physician regarding a potentially fatal outcome. A patient over 50 yr. of age, more commonly a woman, who enters the hospital with a short history of severe upper abdominal pain and presents signs of abdominal tenderness and evidence of peripheral circulatory collapse should be subjected to a serum amylase test as soon as possible. If the serum amylase level is markedly or even moderately elevated, the patient is likely to succumb to pancreatic disease and must be closely watched from day to day. During the hospital stay, signs suggesting serious prognosis are peripheral circulatory collapse and gastrointestinal bleeding. A single normal amylase level must not deter the physician from entertaining a healthy suspicion of pancreatic disease, and although a majority of the fatalities from acute pancreatitis occur within the first 48 hr. of the hospital stay, repeated examination for signs of intra-abdominal abscess must be made. Frequent and repeated serum amylase determinations would aid the clinician in administering the correct form of therapy. Prompt diagnosis of acute pancreatitis by clinical observation and by means of the serum amylase test afford proper immediate treatment and intelligent follow-up care. The patient may be spared unnecessary and often harmful operations.

No definite conclusions as to the cause of death in acute pancreatitis can be reached from the study of this series. Until a thorough understanding of the pathogenesis of the disease is attained, its course must remain somewhat unpredictable.[5] At the present time, the remediable causes of death are most frequently found in the cases with suppurative pancreatitis. Fatal abscess formation with gastrointestinal hemorrhage might be prevented by institution of proper surgical measures.

Conclusions as to the cause of death in interstitial and hemorrhagic pancreatitis also remain speculative. In most instances, the extent of morbid anatomical change within the pancreas does not appear to be sufficient to cause death. Local and distant fat necroses have long been known to represent the effect of fat-splitting

5. Siler, V. E., and Wulsin, J. H.: Monographs on Surgery, New York, Thomas Nelson & Sons, 1950, pp. 115-197.

enzymes liberated from the pancreas in abnormal amounts. Other pancreatic enzymes are also undoubtedly disseminated throughout the blood stream in abnormal concentrations, as is known in the case of amylase. Whether these enzymes, singly or collectively, are responsible for such general signs of toxicity as circulatory collapse and albuminuria is not yet known. Another factor of importance may be the peripancreatic edema and hemorrhage so commonly seen at postmortem examination. This reaction extends to the mesenteries, to the periaortic tissues about the celiac axis and autonomic nerves, and to the periadrenal and perirenal fat. Perhaps acute adrenal insufficiency is responsible for some cases of sudden death in acute hemorrhagic pancreatitis. Irritation of the autonomic nerves and ganglions by the spreading inflammatory reaction may account for the cardiac irregularity seen in electrocardiographic tracings and for the severe pain characteristic of this disease.

Although the problem of the cause of death in acute pancreatitis has not been solved, fatalities can be prevented by (1) surgical drainage of pancreatic abscesses and (2) measures to avoid the development of the hemorrhagic and necrotic form of the disease. The latter often results from improper treatment and unnecessary operations in cases of the mild interstitial type. Careful clinical supervision of the patient after an attack of pancreatitis, and interval cholecystectomy when gallbladder disease is present, will also assist in lowering the incidence of fatal pancreatitis.

SUMMARY

During the 10-year period 1941-1950 inclusive, there were 164 admissions for acute pancreatitis to the Cincinnati General Hospital. The mortality rate within this group was 14.0%, a lower figure than that reported for a similar but smaller series covering the period from 1941 to 1948 inclusive.

A detailed study has been made of 22 fatal cases of acute pancreatitis, with emphasis on the clinical features and the serum amylase determinations. Peripheral circulatory collapse and gastrointestinal hemorrhage were found to be serious prognostic signs.

In 14 cases the correct diagnosis of acute pancreatitis was not established prior to operation or to postmortem examination because of failure to use the serum amylase test or because of improper interpretation of the results. The serum amylase values in fatal cases showed characteristically a moderate and persistent increase rather than an excessively high level.

The clinical course and the cause of death in these cases have been analyzed in an effort to show how fatalities in acute pancreatitis may be prevented.

STUDY OF THE TYPES OF RECURRENCE FOLLOWING INGUINAL HERNIORRHAPHY

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THE OPERATION for the repair of an inguinal hernia is one of the commonest operations performed in both large and small hospitals in this country. In teaching hospitals it is one of the first major operations to be turned over to young surgeons. Strangely enough, this operative procedure is still far from standardized. There are innumerable variations, many of which bear the names of distinguished surgeons. Each variation has been prompted by dissatisfaction with the results previously obtained. The results following the use of the new technique are always an improvement over previous results. Considering the great number of techniques that have been described, one cannot help but wonder whether the better results are due to the new technique or to the fact that the author has made himself, and those exposed to his teaching, a better surgeon. Stimulating interest and studying one particular subject will always improve performance.

The success of any one technique for herniorrhaphy has always been measured by the rate of recurrence, and justly so.[1] There have been many follow-up studies published, with recurrence rates varying. The emphasis has always been on the rate of recurrence, with little importance attached to the type. In fact, recurrences are generally listed only as direct or indirect, and little further details are given.[2] One

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 23, 1951.

1. (*a*) Christopher, P.: The McArthur Operation for Inguinal Hernia, Surgery **21**:482, 1947. (*b*) Mattson, H.: The Use of the Rectus Sheath and Superior Pubic Ligament in Direct and Recurrent Inguinal Hernia, ibid. **19**:498, 1946. (*c*) Glenn, F.: Surgical Treatment of Hernia, Ann. Surg. **125**:72, 1947. (*d*) Garner, A.: Inguinal Hernia, Am. J. Surg. **74**:14, 1947. (*e*) Coley, B.: Three Thousand Consecutive Herniotomies, Ann. Surg. **80**:242, 1924. (*f*) McVay, C.: Inguinal and Femoral Hernioplasty, Arch. Surg. **57**:524 (Oct.) 1948. (*g*) Clear, J.: Ten Year Statistical Study of Inguinal Hernias, A. M. A. Arch. Surg. **62**:70 (Jan.) 1951. (*h*) Blodgett, J., and Beattie, E.: The Effect of Early Postoperative Rising on the Recurrence Rate of Hernia, Surg., Gynec. & Obst. **84**:716, 1947. (*i*) Skinner, H., and Duncan, R.: Recurrent Inguinal Hernia, Ann. Surg. **122**:68, 1945.

2. (*a*) Stein, H., and Casten, D.: A Study of Recurrences Following Inguinal Hernioplasty, Surgery **14**:819, 1943. (*b*) Iason, A.: Why Hernias Recur, Am. J. Surg. **72**:550, 1946. (*c*) Gaston, E.: Living Fascial Sutures in Inguinal Herniorrhaphy, Arch. Surg. **54**:414 (April) 1947. (*d*) Burton, C., and Raoul, R.: The Results of Surgical Treatment of Recurrent Inguinal Hernia, Surg., Gynec. & Obst. **70**:969, 1940. (*e*) Craig, C.: Further Experiences with the Inversion Operation for Indirect Inguinal Hernia, M. J. Australia **1**:19, 1950. (*f*) Pattrick, W.: Recurrent Hernia, Brit. J. Surg. **31**:231, 1944. (*g*) Shelley, H.: Recurrent Inguinal Hernia, Arch. Surg. **41**:1437 (Dec.) 1940. (*h*) Fallis, L.: Recurrent Inguinal Hernia, Ann. Surg. **106**:72, 1937. (*i*) Doran, F., and Lonsdale, W.: A Simple Experimental Method of Evaluation for the Bassini and Allied Types of Herniorrhaphy, Brit. J. Surg. **36**:339, 1949.

exception is the article by Skinner and Duncan,[11] in which detailed drawings are presented of five types of recurrences.

Recent personal experiences showed faults of our previous operations which were much more specific than the terms indirect or direct recurrence can indicate. Because of this informative criticism gained, it was decided to investigate the records of the last 100 recurrent hernias reoperated on at St. Joseph's Mercy Hospital in Ann Arbor. Fortunately, because of the pressure brought to bear on the staff in meeting the standardization requirements of the American College of Surgeons and the American Medical Association, the operator's notes are now well written and detailed. This has allowed us to describe accurately the type of recurrence found at reoperation. As the recurrence may be considered the indication of a technical error [3] in the original operation, we felt that information had been gained which might benefit those doing inguinal herniorrhaphies.

Follow-up statistics after herniorrhaphy usually cover three to five year periods. A recent exception is the report of Clear,[1g] who emphasizes the importance of a 10-yr. follow-up. He found that 44 of 114 recurrences occurred 5 to 10 yr. after operation. The right to criticize a repair which has held for 5, 10 or even 30 yr. before breaking down may well be questioned. There are those who believe that any hernia appearing after five years is a new and not a recurrent hernia. If so, it should take the form of one of the classical primary hernias. The consensus from the literature would seem to be that any inguinal hernia appearing at the site of a former herniorrhaphy must be considered a recurrent hernia.[11] For the purpose of this record study, such a stand is taken. During the period studied, 116 recurrent inguinal hernias were reoperated on, but 11 cases were discarded because of insufficient information, leaving 105 for this report.

Fifty-one per cent of the hernias recurred within one year of operation, 24% within five years and 25% after five years. The longest period was 32 years. Fourteen patients had undergone one or more previous operations for recurrent hernia. There was no correlation found between the time of recurrence after the previous operation and the type of recurrence. However, as will be shown later, there was a possible correlation between the length of time that the recurrence was present before reoperation and the type of recurrence found. The average age of the patients was 53 years. There was no correlation between the type of recurrence found and the age of the patient. Many causes have been given for recurrence, such as failure to remove the sac or to recognize a second hernia,[4] obesity and body build of the patient, postoperative complications, anesthesia and choice of suture material.[5] However, the basic factor is generally admitted to be the surgical technique employed.[6] Because this paper is not a follow-up study, it is not within its scope to criticize or compliment any one surgical technique. The recurrences here reported followed the surgical techniques popularly used at the time of the original operation. A tabulation of the type of the original operations would serve no useful purpose and would unjustifiably criticize the more modern techniques. There was no corre-

3. Kilbourne, B. C.: Critical Study of 50 Recurrent Hernias, Indust. Med. **20**:83-84, 1951. Fallis.[2h]

4. Stein and Casten.[2a] Burton and Raoul.[2d] Pattrick.[2f]

5. Wilmoth, C.: The Recurrent Inguinal Hernia, Surg., Gynec. & Obst. **71**:802, 1940 Coley.[1e] Iason.[2b]

6. Doyle, R.: Recurrent Inguinal Hernia, Rev. Gastroenterol. **17**:563, 1950.

lation between the type of the recurrence and the type of the original operation. It has been pointed out that direct hernias constitute only about 10% of the original hernias seen, but direct recurrences have been reported in as high as 90% of the cases.[7] We cannot report any correlation between the type of the original hernia and the type of the recurrence found.

The types of recurrence found in this record study have been classified, as shown in the table. Those at the internal ring, accounting for 52%, fell into three distinct subgroups. Group A presented a sharply localized recurrence at the internal ring, Group B were above and lateral to the ring and Group C were the classical well developed indirect inguinal hernias. The direct area of the canal was considered sound in all cases. In Type II, accounting for 23% of the recurrences, there was a sharply localized defect at the pubic tubercle. The direct area and the internal ring were sound. Type III, with 24% of the recurrences, represents a complete breakdown of the floor as a typical direct hernia. The average time these recurrences were present before reoperation is of interest. As seen in the table, Type Ia had been present for an average of 2.6 yr. However, if one case in which the recurrence had

Classification of 105 Recurrent Hernias

Type of Recurrence			Average Duration of Recurrence, Yr.
I. At internal ring			
a. Small at ring	19		2.6 or 1.5
b. Above and lateral	12		1.6
c. Typical indirect hernia	21		3.3
		52	
II. At pubic tubercle		23	2.6 or 1.5
III. Direct hernia		24	6.6
IV. Miscellaneous		6	1
		105	

been present for 26 yr. is eliminated, the average is 1.5 yr. Group Ib had been present for 1.6 yr. and Group Ic for 3.3 yr. Group II had been present for an average of 2.6 yr., but if one patient who used a truss successfully for 25 yr. is eliminated, the average is 1.5 yr. The group of patients with direct recurrences waited an average of 6.6 yr. before reoperation. Although these groups are small for statistical purposes, it would seem that there might be some significance in the time factor in that the longer a recurrence is allowed to exist the greater the weakness. Perhaps some of the large indirect or direct recurrences started as small localized defects at the internal ring or at the symphysis pubis.

Figure 1*A* is an artist's concept of the localized recurrence at the internal ring. Figure 1*B* shows the recurrence above and lateral to the ring. In both types the previous repair was solid except for these defects. Closure of the defect was all that was needed. Figure 1*C* shows the typical well developed indirect inguinal hernia. The direct area was solid. These 52 cases out of the 105 represent failure at the original operation to close the internal ring adequately. Figure 2 demonstrates the sharply localized defect at the pubic tubercle or the lower end of the canal floor. After excision or invagination of the sac, one or two stitches closed this defect. The canal floor and the internal ring were sound, indicating that the original error in technique had been made with the first stitch taken. Therefore, in 75% of these

7. Glenn.[1c] Burton.[2d] Fallis.[2h]

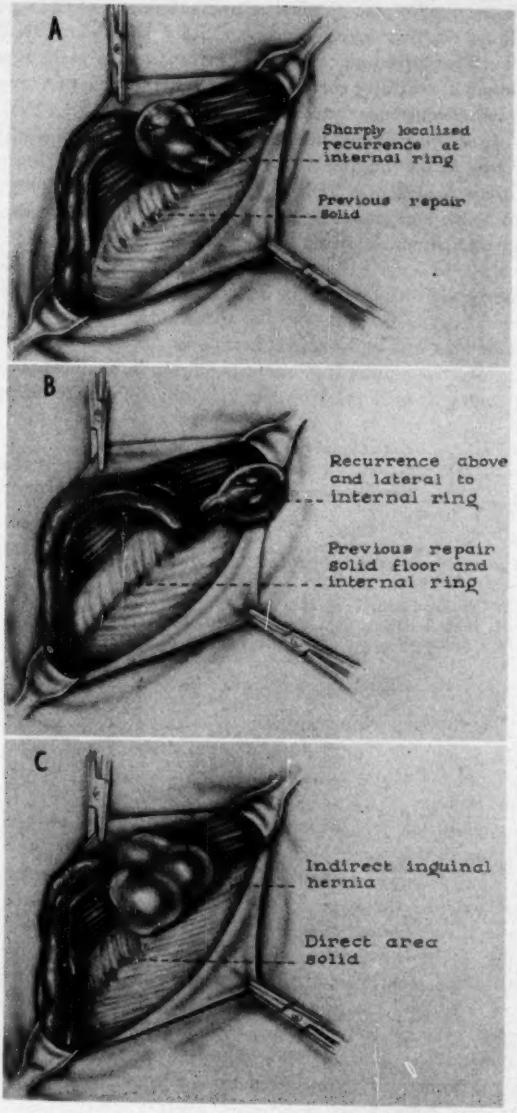

Fig. 1.—*A*, recurrence at inguinal ring (19% of recurrences; average duration, 2.6 or 1.5 yr.). *B*, recurrence above and lateral to internal ring (12% of recurrences; average duration, 1.6 yr.). *C*, recurrence as typical indirect inguinal hernia (21% of recurrences; average duration, 3.3 yr.).

recurrences it would seem that the error at the original operation had been in failure to obtain an accurate closure of the internal ring and a firm first stitch at the pubic tubercle. These principles, along with high ligation of the indirect sac, are basic concepts in all descriptions of hernia repair. It would appear to us that individual surgeons should use the surgical technique which best allows them to fulfill these basic concepts. We should like to enter a plea for early reoperation on recurrent

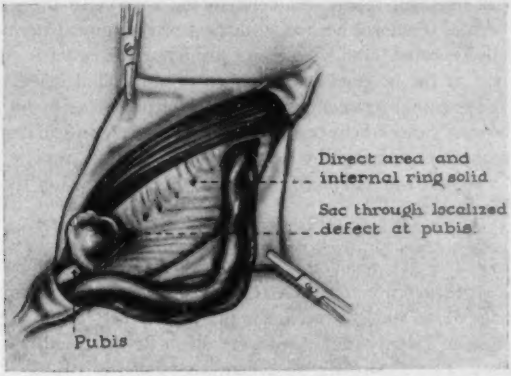

Fig. 2.—Recurrence at pubis (23% of recurrences; average duration, 2.6 or 1.5 yr.).

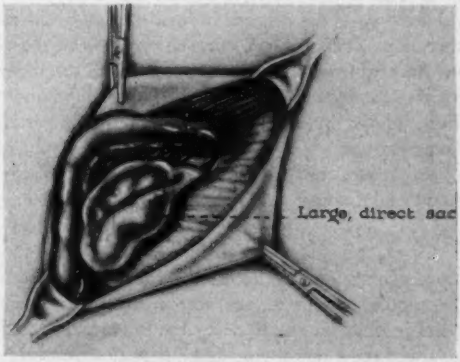

Fig. 3.—Complete, direct recurrence (24% of recurrences; average duration, 6.6 yr.).

hernias because we are convinced that an appreciable number of large direct or indirect recurrences start as small defects. In well over one-half of the cases studied, after excision of the recurrent sac only one or two stitches were needed for repair. It was unnecessary to tear down the entire area, because the defect was still sharply localized.

Figure 3 illustrates the complete breakdown of the canal floor, which accounted for 24% of the recurrences.

The miscellaneous group of six cases is of interest. In two there was a localized recurrence at both the pubic tubercle and the internal ring. In another two cases there was a localized break-through in the middle of the canal floor. These were early recurrences and were repaired within six months. Undoubtedly if they had been allowed to exist for five or six years they would have progressed to full direct recurrence. In one case only there was no evidence that any repair had been done previously. In the sixth case there was a recurrence over the femoral vessels. The previous Cooper ligament repair was solid to the vessels, so the lesion was not a true femoral hernia. Femoral hernias occurring after inguinal herniorrhaphy have been occasionally reported [8] and have been considered due either to a femoral hernia that was present at the original operation or to surgical damage to the inguinal ligament. If the inguinal ligament is so poor a structure as many authors would have us believe, one cannot help but wonder why recurrences under it do not take place more frequently. During the period studied for this report, there were 36 femoral hernias repaired at St. Joseph's Mercy Hospital. Two of these followed an inguinal herniorrhaphy.

SUMMARY

One hundred and five recurrent inguinal hernias were studied and classified as to the type of recurrence found at reoperation. Fifty-two hernias recurred at the internal ring, 31 as small defects. Twenty-three were due to a small defect at the symphysis pubis. Twenty-four cases were direct hernias, with a complete breakdown of the floor. There were six miscellaneous types.

Because this is not a follow-up study, criticism of any one surgical technique is not offered. A tabulation of the original operations is not given, as it would serve no purpose. No correlation can be reported between the type of recurrence found at reoperation and the type of the original hernia, the age of the patient, or the type of the original operation. There was no correlation between the type of recurrence found and the time interval from the original operation to the recurrence. However, there may be a relation between the type of recurrence found and the length of time the recurrence was endured by the patient, in that the longer the recurrence the larger the defect tended to be.

It is pointed out that 75% of the recurrences were due to failure either to close the internal ring or to take a firm stitch at the symphysis pubis.

CONCLUSIONS

The answer to the question, "What is the cause of recurrence after inguinal herniorrhaphy?" is not as simple as the accompanying drawings might indicate. However, we do feel justified in emphasizing the importance of the basic principles of an accurate closure of the internal ring and a firm closure at the symphysis pubis. If these principles are followed, one may use any surgical technique desired.

8 Brown, R., and Haynes, L.: Recurrent Inguinal Hernia. U. S. Nav. M. Bull. **47**:1053, 1947. Coley.[10]

SLOW VERSUS RAPID INTESTINAL STRANGULATION OBSTRUCTION

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OUR EXPERIMENTS were undertaken to investigate the phenomenon of slow intestinal strangulation, to compare it with that of rapid intestinal strangulation, and to observe the effects of a combination of the two. There has been a paucity of experimental investigation along these lines despite the fact that these phenomena undoubtedly occur in one combination or another in strangulation obstructions in the human. To the best of our knowledge, the only work directly applicable to this problem is that of Goldman.[1] In 1943 he reported an experiment in dogs in which a loop of ileum was stretched over a taut string. This produced venous stasis and edema in the loop, and arterial pulsations ceased after some three or four hours. Gaseous distention as determined by roentgenologic studies was absent in 25% of the animals either in the involved loop or in the proximal ileum.

EXPERIMENTAL DATA

Rapid Strangulation; Control Series.—For the past several years experimental intestinal strangulations of many types have been produced in this laboratory for studies with widely divergent purposes. In order to standardize the approach to the present problem and for a new control series, we produced rapid strangulations with binding tape in a rather exact manner in eight dogs. With the animals under light pentobarbital (nembutal®) sodium anesthesia, a 30 cm. loop of distal ileum was bound with binding tape until the arterial pulsations ceased. The tape was secured at this point, and the return of pulsations was awaited. If they did not return, the tape was slightly loosened. In each instance the pulsations were noted to disappear within a few minutes after their return. The loop became cyanotic and moderately distended within two minutes. It was then returned to the abdomen and the incision closed. Blood was taken before surgical intervention and at regular intervals afterward for antilecithinase studies. The details of our findings in this control group in comparison with the other groups will be discussed.

Aided by a grant from the Grunow Surgical Fund.

From the Department of Surgery, Northwestern University Medical School.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 24, 1951.

1. Goldman, L.: Intestinal Strangulation Obstruction with Negative X-Ray Findings, Surgery **13**:834-846, 1943.

Slow Strangulation; Preliminary Studies.—In 13 dogs an attempt was made to produce slow strangulation by applying binding tape to a loop of distal ileum just tight enough to cause slight venous congestion. In this preliminary group of animals only longevity studies and postmortem gross and microscopic studies were made.

Four of these animals died of spontaneously superimposed rapid strangulation obstruction within three days. Five died with evidence of simple intestinal obstruction proximal to the loop in three to seven days. Two dogs died between the 7th and 29th days, one with strangulation obstruction and one with only simple obstruction. The remaining two dogs were killed at 30 days and were found to have small gray, shrunken loops with marked proximal distention. Thus, superimposed rapid strangulation occurred in five of 13 animals at various times. The involved loop in the other animals was always smaller than expected, contracted, pinkish gray and viable.

Histological sections were taken in all instances from the proximal bowel, involved loop and distal bowel. Microscopic study of the tissues in dogs not dead of strangulation revealed a varying degree of muscular hypertrophy as well as degenerating mucosa, with spotty necrosis of the latter in both the proximal intestine and the involved loops. Bacterial stains made according to Glynn's modification of the Gram stain showed bacteria in the walls of both the proximal intestine and the involved loop. Similar studies of the necrotic strangulated loops showed large numbers of bacteria.

Whether sudden superimposed strangulation would occur or not appeared unpredictable, and if it did occur, the time of occurrence could not be foreseen. This observation has obvious clinical implications which will be discussed later. We had the impression from this group of animals that when rapid superimposed strangulation occurred, death of tissue progressed more rapidly than in our control series. Therefore, our next step was to determine the validity of this impression and to understand better the train of events which led to this situation. Hence, the next series of experiments was undertaken.

Rapid Strangulation Superimposed on Slow Strangulation.—A group of 20 dogs was subjected to slow strangulation for 24 hr. by placing a binding tape loosely about a 30 cm. loop of distal ileum. The tape was placed considerably more loosely in these animals than in the previous series so that the loop showed no evidence of circulatory embarrassment. Seven dogs were killed at 24 hr. for microscopic and bacterial studies. In the remaining 13 dogs, after 24 hr. of slow strangulation, a second laparotomy was performed with the animals under very light pentobarbital sodium anesthesia and a second binding tape was placed carefully over the initial one and tightened until all pulsations in the involved mesentery ceased. As in the control series, the pulsations always returned and persisted for a length of time ranging from about one to three minutes. The loop invariably turned cyanotic rapidly. After the loop was studied for periods up to one and a half hours, it was returned to the abdomen and the abdominal wall closed. Food was withheld for 24 hr., but water was given. After this period the animals were allowed to eat at will.

Blood was withdrawn before the slow strangulation was induced and daily thereafter for antilecithinase studies and hematocrit determinations. On the death of each animal histological sections were taken for microscopic and bacterial studies.

When such rapid strangulations were superimposed on slow strangulations, we invariably observed a faster occurrence of events leading to gangrene than in the control series of acute strangulations. Within 15 min. the loop showed evidence of a much more intense hemorrhagic infiltration than that in the controls. By one hour the loop appeared to be irreversibly infarcted as evidenced by its intense, black and edematous appearance and the complete blood soaking of the involved

Fig. 1.—Typical microscopic appearance of intestine after 24 hr. of slow strangulation. Note the remarkable dilatation of the lymphatic channels extending from the tip of a villus through the submucosa into the muscularis. The lower layer of mucosa contains red cells and a few polymorphonuclear leukocytes in the specimen, but in other specimens almost no extravasation occurs at this stage. × 95.

mesentery. By contrast, the loops in the control series of strangulations did not exhibit this appearance until after six hours. Even after six hours of initial rapid strangulation, release of the binding tape will result in recovery in certain circum-

stances.[2] None of the loops subjected to superimposed strangulation was viable at the end of one hour.

Another difference was the fact that the degree of distention in the loop in the superimposed strangulations was considerably less than that which we were accustomed to seeing in the control series. There was also a difference in the appearance of the mesentery; in the superimposed type the mesentery was completely blood-soaked and highly edematous after one hour, whereas in the control series the mesenteric extravasation remained, for the most part, perivascular.

If animals subjected to these superimposed strangulations were not killed and were allowed to die otherwise, the appearance of the involved loop at death was

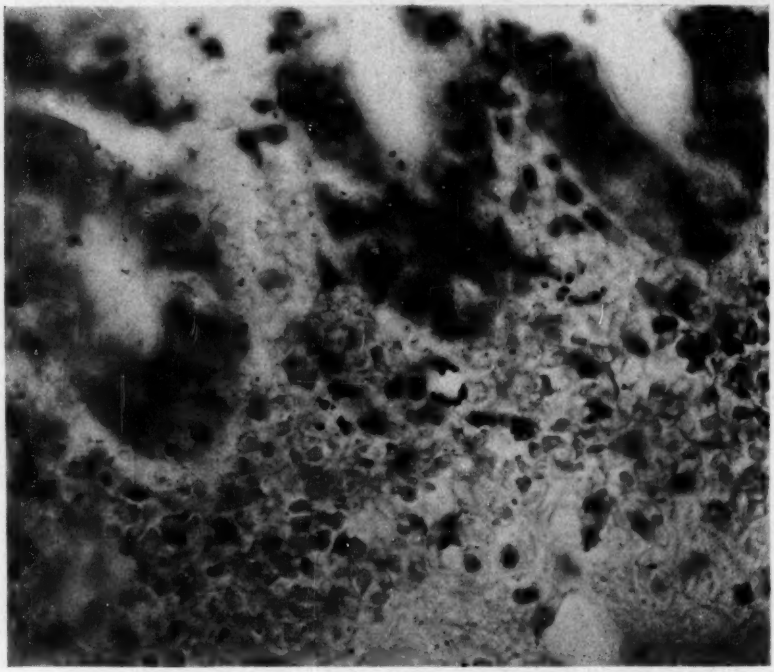

Fig. 2.—Bacterial stain of lower layers of mucosa after 24 hr. of slow strangulation. Note the bacteria in the walls of the lymphatics as well as in other areas. The bacteria at this stage are mostly cocci. × 875.

remarkably different from that of the control series. Instead of the usual moderately distended black loop in the control series of rapid strangulations, these animals exhibited a loop which was actually necrotic, greenish black, friable, and almost gelatinous in consistency. When perforations occurred in the control series they were usually punctate and were located in the paramesenteric or antemesen-

2. Laufman, H.: Experimental Evidence of Factors Concerned in the Eventual Recovery of Strangulated Intestine: Effects of Massive Penicillin Therapy, Surgery **28**:509-515, 1950.

teric portions of the bowel. In the superimposed strangulations, however, there was actually gross disruption of tissues with much larger openings, in some instances practically transecting the loop. In the control series only 25% of the animals showed gross evidence of necrosis of the involved loop at the time of death. Of the animals with superimposed strangulations 75% showed gross evidence of necrosis and the severe type of degeneration described above.

Regarding longevity, the average in these animals was 40 hr., with a range of 12 to 104 hr., after the superimposed rapid strangulation, while in the control group with initial rapid strangulations the average longevity was 52 hr., with a

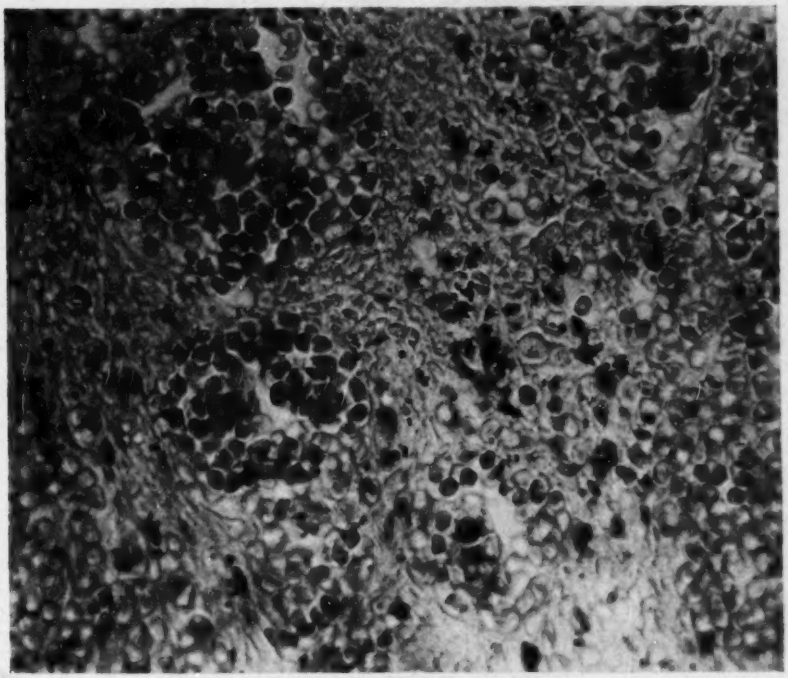

Fig.3.—Bacterial stain of wall of bowel after 24 hr. of initial rapid strangulation. Note the numerous clumps of cocci. × 875.

range of 26 to 79 hr. Although these figures are obviously not significant on a statistical basis, it would appear that in general animals with a strangulation superimposed on a previous slow strangulation died somewhat more rapidly than animals with only an initial rapid strangulation.

Histological sections taken from seven animals after 24 hr. of slow strangulation showed a remarkable dilatation of the lymphatic vessels of the bowel wall. These dilated lymphatic vessels were traced from the tip of the villi to the serosa of the bowel. Dilation occurred before extravasation of blood into any of the layers of

the bowel. We believe that this stage of lymphatic engorgement has been hitherto overlooked in strangulation obstruction, since histologic sections have not been taken early. As a rule, by the time sections are taken from strangulated loops there has been such extravasation of blood cells into the mural structures that the initial lymphatic engorgement is no longer observable. It can readily be seen that if the tip of a villus containing such a lymphatic vessel becomes eroded, there is a direct

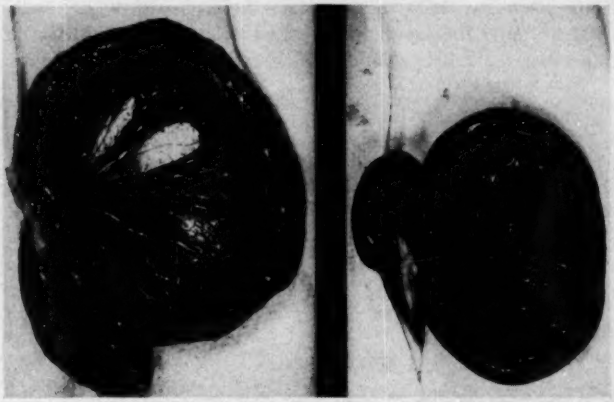

Fig. 4.—Comparison of gross appearance between initial rapid strangulation (left) and 24-hr. slow strangulation with superimposed rapid strangulation (right). These photographs were taken one hour after rapid strangulation in each instance. Note the much more intense hemorrhagic infiltration and nonviable appearance of the loop with the superimposed strangulation. The loop on the left is still viable. The loop on the right is nonviable.

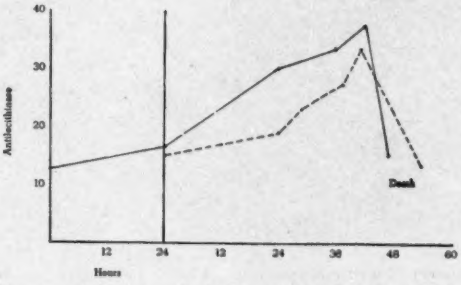

Fig. 5.—Typical curves of serum antilecithinase titers following initial rapid strangulation as compared with rapid strangulation superimposed on 24-hr. slow strangulation. Broken line is for Dog 6, with initial rapid strangulation, and solid line is for Dog 22, with superimposed strangulation.

pathway for absorption of bacterial products from the lumen. The phenomena of lymphatic distention and clubbing of villi have been observed in simple obstruction.[3]

3. Gage, M., and Hosoi, K.: Histological Changes Observed in the Intestinal Wall Following Simple Mechanical Obstruction in Rabbits, Proc. Soc. Exper. Biol. & Med. **32**:1651-1653, 1935.

Bacterial stains, made at various stages, show that large numbers of bacteria invade the wall while it is still grossly viable and rather normal in appearance. These bacteria appear first in the endothelial cells lining the dilated lymphatic vessels. Shortly thereafter large numbers of bacteria are seen, chiefly in the lower mucosa and submucosa. Also, in these areas the first extravasation of erythrocytes appear as well as a moderate degree of polymorphonuclear leucocytic exudate.

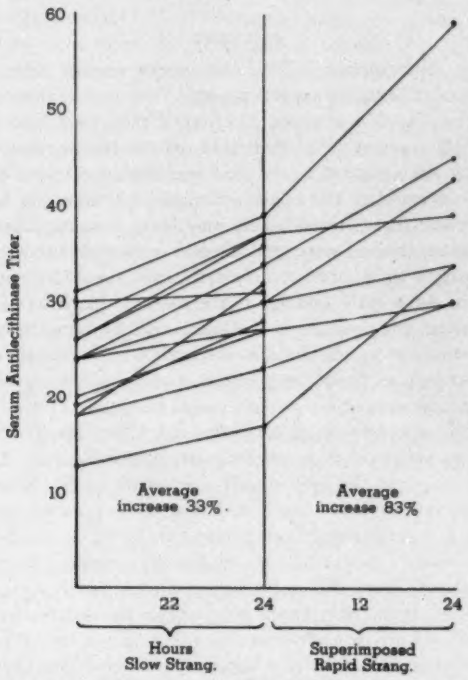

Fig. 6.—Comparison of alterations in serum antilecithinase titers following 24 hr. of slow strangulation and 24 hr. of superimposed rapid strangulation.

Summary of Data

	No. of Dogs	Survival, Hr.	Gross Necrosis	Average Increase in Antilecithinase Titers
Initial rapid strangulation	8	52	25%	81%
Rapid strangulation superimposed on slow strangulation	20	40	75%	83%
Control	..	..	....	33%

Antilecithinase Studies.—The average antilecithinase titer of 20 "normal" mongrel dogs was 24 units, as determined by the method used by Tanturi and his associates.[4] After laparotomy alone we found an average increase of 33%. After 24 hr. of slow strangulation the antibody titer was essentially unchanged from that following laparotomy alone. However, after 24 hr. of superimposed rapid strangulation, the antilecithinase titer rose on an average of 83% above the preoperative average and 50% above the level following slow strangulation. The increase in antilecithinase titers following rapid strangulation alone averages 81%.

COMMENT

When a slow strangulation occurs, one cannot predict when a spontaneous rapid strangulation will become superimposed. This may be due to one of several reasons or to a combination of them. Peristaltic movement may cause the compression of a larger segment of intestine into the constricting ring, and the edema at the constricting site pursuant to the slow occlusion may cause further constriction of the involved vessels. The obvious clinical implication lies in the possibility that an asymptomatic incarcerated hernia may become strangulated at any time.

When slow strangulations were controlled in our experiments, we were able to observe early changes which are not ordinarily seen in rapid strangulations. The most important of these early findings is the marked dilatation of the intramural lymphatic vessels and the invasion of the lining cells by bacteria. We feel that it is of some importance to emphasize our observation that bacteria invade the wall of an incarcerated loop of bowel long before it shows color changes indicative of circulatory embarrassment.

It has been common knowledge for some time[5] that short strangulated loops are more prone to perforate than are long strangulated ones. Our experiments indicate that the length of the loop is only one factor in the question of whether the loop will perforate or not. We found that when a rapid strangulation was superimposed on a slow strangulation, perforation occurred in 75% of the loops, with massive necrosis of tissue. Loops of identical length (30 cm.) when subjected to initial rapid strangulation showed perforations of only punctate nature in 25% of the cases. It therefore seems obvious that the degree of necrosis and the question of perforation are dependent, among other things, on the presence of slow strangulation for some time prior to a superimposed rapid strangulation. During the period of slow strangulation there is a definite invasion of viable mural structures by bacteria. This is apparently the crucial factor in the rapid disintegration of the involved loop once rapid strangulation is superimposed. These findings could account for the extremely rapid onset of gangrene in some cases of strangulated hernia.

Since the demonstration by Tanturi and his co-workers[6] of the presence of lecithinase (toxin of the type A Clostridium welchii) in the abdominal and intra-

4. Tanturi, C.; Swigart, L. L., and Canepa, J. F.: Prevention of Death from Experimental Ligation of the Liver (Hepatic Proper) Branches of the Hepatic Artery, Surg., Gynec. & Obst. **91**:680-704, 1950.

5. Holt, R. L.: The Pathology of Acute Strangulation of the Intestine, Brit. J. Surg. **21**:582-603, 1934.

6. Tanturi, C.; Anderson, R. E., and Canepa, J. F.: Lecithinase and Hyaluronidase in Experimental Intestinal Obstruction, Surg., Gynec. & Obst. **90**:171-174, 1950.

luminal fluid of strangulated intestinal loops, the question of the importance of this toxin in the toxicity of strangulation obstruction has been under investigation. We have demonstrated lecithinase in the thoracic duct lymph of animals with intestinal strangulation and therefore have inferred that the toxin reaches the circulation.[7] However, the presence of the toxin in the blood stream cannot be detected until the hematocrit approaches zero. Theoretically, this is due in part to the rapidity of enzymatic actions and in part to the competition for the binding radicals of lecithinase by substrate and by antitoxin.

The present antilecithinase studies were undertaken on the premise that most mongrel dogs, having been subjected at one time or another during their previous existence to trauma of various types, possess an antibody (antilecithinase) titer. Since antilecithinase is an easily measurable entity in the blood stream, this approach seemed practical. If the naturally occurring antitoxin is exposed to toxin, variations in the former can be interpreted as being imposed by the latter. If antibodies already exist prior to the formation of the toxin, as was found in all of our mongrel dogs, the antibody titer, instead of diminishing on absorption of the toxin, would in such dogs be expected to rise because of the anamnestic reaction.[8] However, if very large amounts of toxin were introduced suddenly, it would be expected that the antibody titer would no longer be able to rise in proportion and would drop precipitously. We found this pattern to occur in all animals with rapid strangulations whether it was superimposed on a previous slow strangulation or not.

During the period of slow strangulation no demonstrable toxin was absorbed despite the invasion of the wall by bacteria. It is entirely possible that other toxins for which we have no tests of measurement at present are absorbed during the earlier phases of strangulation. However, it appears that a combination of massive bacterial invasion and dead tissue is necessary for a detectable absorption of lecithinase.

Our experiments indicate that the period of slow strangulation is important in the eventual outcome of a strangulated loop of intestine. When a rapid strangulation is superimposed on a slow strangulation, the involved intestinal tissue becomes gangrenous much more rapidly than in initial rapid strangulation.

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7. Laufman, H.; Tanturi, C., and Furr, W. E., Jr.: Recovery of Bacterial Enzymes from the Thoracic Duct in Strangulation Obstruction, in Forum Papers, Philadelphia, W. B. Saunders Company, 1951.

8. Boyd, W. C.: Fundamentals of Immunology, New York, Interscience Publishers, Inc., 1943, pp. 64-65.

CIRCULATORY DISTURBANCES PRODUCED BY ACUTE INTESTINAL DISTENTION IN THE LIVING ANIMAL

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HERBERT J. ROBB, M.D.
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LYLE F. JACOBSON, M.D.
DETROIT

THE EFFECT of distention on the intestinal circulation has been a matter of interest to surgical investigators for many years. The problem has been approached from many angles and by varied techniques. Since studies of the human situation in life are not possible by presently available techniques and since most of the animal experimentation has been carried out on dogs, whose intestinal morphology and vasculature differ greatly from those of man (Noer,[1] Noer, Derr and Johnston[2]), it has appeared worth while to reinvestigate the problem by newer techniques in an animal whose circulation may be considered more nearly comparable to that of the human being. This presentation describes findings obtained through quartz rod transillumination studies of the circulation in the living rabbit intestine during increasing increments of distention.

Previous investigations of the effects of distention on the intestinal circulation have been many, and a number of the reports were reviewed in a previous report from this laboratory (Noer and Derr[3]). Among the studies referred to in that paper particular mention should be made of the work of Van Zwalenburg,[4] who in 1907 inserted a cannula carrying a small lamp into the lumen of the dog intestine as a means for studying the effect of increased pressure on the blood flow through the intestinal wall. He reported capillary arrest at 30 mm. of mercury, arrest of small veins and slowing of other elements at 60 mm. and almost complete interruption at 90 mm., though his pressures were carried much higher than this before

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From the departments of surgery and anatomy, Wayne University College of Medicine.

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This investigation was supported by a research grant from the Division of Research Grants and Fellowship of National Institutes of Health, United States Public Health Service.

1. Noer, R. J.: The Blood Vessels of the Jejunum and Ileum: A Comparative Study of Man and Certain Laboratory Animals, Am. J. Anat. **73**:293-334, 1943.

2. Noer, R. J.; Derr, J. W., and Johnston, C. G.: The Circulation of the Small Intestine: An Evaluation of Its Revascularizing Potential, Ann. Surg. **130**:608-621, 1949.

3. Noer, R. J., and Derr, J. W.: Effect of Distention on Intestinal Revascularization, Arch. Surg. **59**:542-549 (Sept.) 1949.

4. Van Zwalenburg, C.: Strangulation Resulting from Distention of Hollow Viscera, Ann. Surg. **46**:780, 1907.

absolute cessation of flow was obtained. Oppenheimer and Mann [5] in 1943 reported on direct observations of the intestinal wall of rats made by means of a quartz rod technique similar to that used in the present investigation. They found no change in the capillary circulation at pressures of 10 to 20 mm. of mercury, interference with capillary flow between 30 and 50 mm. of mercury, continuing flow only in the largest vessels at 60 mm., and complete interruption of circulation at about 80 mm. of mercury. A previous report from our laboratories (Noer and Derr [2]) was based on India ink injections of the intestinal vessels during varying degrees of pressure applied by means of a balloon within excised human intestinal loops. These showed no injection of the mural vessels during distending pressures above 70 mm., gradual filling during deflation from 60 or 50 mm. downward, but absence of capillary injection until after deflation was completely accomplished. These studies bear a direct relation to the present report and served as an indication of what might be expected, though species differences are so great that one cannot predict with any confidence the outcome of similar experimental work in other animals.

The rabbit was chosen as the subject of this investigation for several reasons (though some dogs have been studied for comparison). The rabbit vasculature is similar to that of the human small intestine with respect to both the mesenteric circulation and the vasculature within the intestinal wall. The thin intestinal wall of the rabbit also makes it well adapted to transillumination studies. The fact that the rabbit does not vomit and that it is not a hardy animal, while disadvantageous in continuing experimental work, did not particularly hamper investigations of the type recounted here. The heavy muscular wall of the dog intestine, the abundant mesenteric border arterial anastomosis (absent in man), and the plexiform type of intramural anastomoses all militate against choice of this animal for circulatory studies.

APPARATUS

The apparatus utilized in this investigation is similar to that described by Knisely,[6] Hoerr,[7] and others. The particular demands of this problem have necessitated many modifications which will be reported in detail elsewhere. The apparatus is illustrated diagrammatically in Figure 1, and as it actually appears in Figure 2. To maintain physiologic conditions as nearly as possible and to minimize the distracting influence of building vibration the apparatus is set up in an air-conditioned basement room with a concrete floor. The animal is placed on a table constructed of boiler plate, utilized for its weight and resultant inertia, suspended on rubber mounted "in shear" rather than "in compression." A lucite holder is so arranged as to permit uninterrupted maintenance of the mesenteric circulation while the loop for study is held within a channel which can be kept reasonably moist (this holder

5. Oppenheimer, M. J., and Mann, F. C.: Intestinal Capillary Circulation During Distention, Surgery **13**:548-554, 1943.

6. Knisely, M. H.: A Method of Illuminating Living Structures for Microscopic Study, Anat. Rec. **64**:499-524, 1936; An Improved Fused Quartz Living Tissue Illuminator, Anat. Rec. **71** (No. 4):503-508, 1938.

7. Hoerr, N. L.: Illumination of Living Organs for Microscopic Study, in Glasser, O.: Medical Physics, Vol. 1, Chicago, Year Book Publishers, Inc., 1944, pp. 625-627.

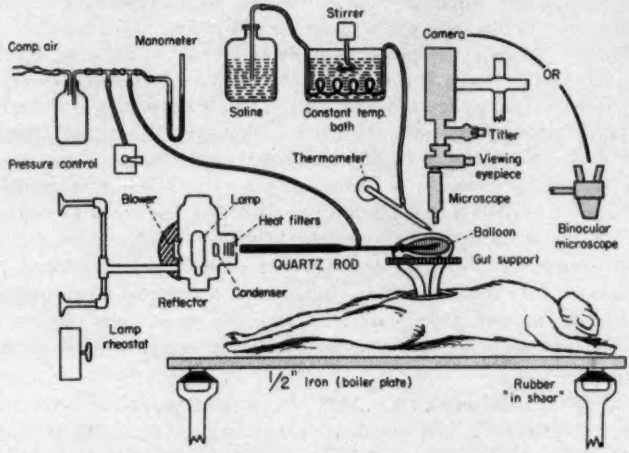

Fig. 1.—Diagrammatic representation of the apparatus for quartz rod transillumination studies as used in this investigation.

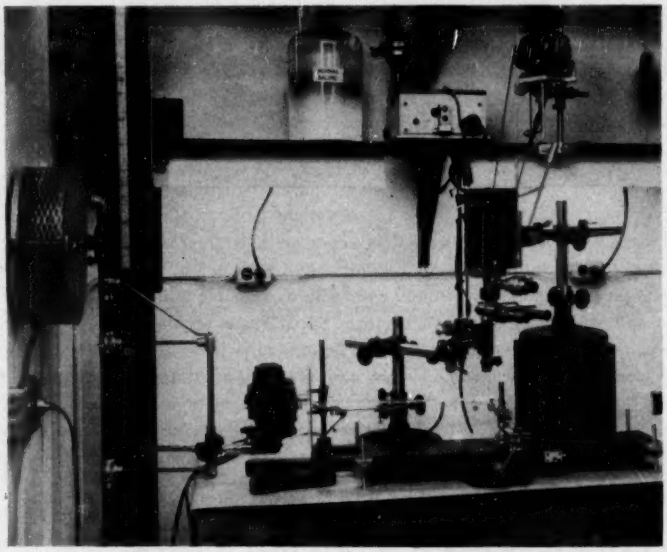

Fig. 2.—Photograph of the apparatus shown in the diagram (Fig. 1). (In this case set up for cinephotomicrography.)

amounts to an open modification of the Zintel chamber.[8] The gut holder is mounted on a rack and pinion mechanism to allow fine focusing without disturbing the camera-microscope relationship.

The illuminating system consists of a 750 or 1,000 watt projection bulb cooled by a flow of air, with a reflector and condensing lenses to focus the beam. (These needs of the illuminating system have been rather easily met by slight modifications of a motion picture projector, the size of the 16 mm. frame fortunately being approximately the size of the base of the quartz rod.) A rheostat to control the degree of illumination makes it possible to carry on observations at lower light levels which generate little heat, the light being increased only for photography.

The quartz rod itself is supported in clamps mounted on the table in such a way that it is separate from the illuminating unit and thus does not receive transmitted vibrations from the blower. Its base is held at the focal point of the light beam. The tip of the quartz rod is cannulated, and a balloon is placed about its tip. A compressed air system with a fine pressure-regulating mechanism is connected to the cannulated rod to provide for controlled inflation of the balloon, with pressures measured by a mercury or water manometer.

Physiologic conditions are maintained as nearly as possible by surrounding the gut in the lucite holder with cotton pledgets moistened in isotonic sodium chloride solution and by constantly maintaining a flow of this solution at a constant temperature onto the surface of the gut so that there can be no drying of the exposed serosa.

Observations are carried on by means of a wide field binocular dissecting microscope, but arrangements are provided for substituting an apparatus for cinephotomicrography. The latter includes a beam-splitting eyepiece, which makes it possible to view the field at the same time photography is carried on. A titler is also added so that the degree of intraintestinal pressure can be photographed onto the film at the exact time of photography, thus avoiding mistakes which might occur if the record depended on a simultaneously kept ledger. Cinephotomicrography has been used in order that the changes, which take place rather rapidly, may be recorded for repeated study. One is thus enabled to review repeatedly the changes as they are produced by different pressures and thus to evaluate the results far more accurately than would be possible by single observations carried out through the dissecting microscope.

This apparatus at first glance appears rather complex. It has been evolved step by step during the course of the experimentation, and each added component of the apparatus has been provided to meet a definite need. It is our feeling that all of the elements described are essential, and in our hands the apparatus as illustrated is now a practical and workable one for this particular type of observation.

TECHNIQUE

The animals are lightly anesthetized with intravenous injection of pentobarbital (nembutal®) sodium. A small abdominal incision is made and a loop of small bowel drawn out and placed into the lucite holder in such a manner that circulation through the mesentery is not disturbed. As described above, the gut is then surrounded by moist pledgets and the flow of isotonic sodium chloride solution at body

8. Zintel, H. A.: A New Transparent Chamber for Exteriorizing a Loop of Intestine and Its Mesentery, Anat. Rec. **66**:437-447, 1936.

temperature is begun. It is important that the nondistended intestine be carefully studied for a brief period to be sure that the material is satisfactory for study. Trauma, initially present, must always be considered as an indication for discontinuance of the experiment, for it would be impossible to interpret the findings adequately in the presence of trauma not incident to the experiment itself. Evidences of trauma are either gross or microscopic hemorrhage in the intestinal wall or intravascular agglutination of blood cells ("sludging"). The presence of either of these factors prohibits use of the particular animal showing them. The blood flow should be even and normally present in all elements of the circulation, and capillaries should function in their normally intermittent manner. If all these conditions have been met, the intestine is distended by successive increments of 5 or 10 mm. of mercury (or like amounts of water), and observations at each level of pressure are recorded. Ideally these findings are recorded on motion picture film, to permit repeated study of the circulatory responses. From time to time the intraluminal pressure is returned to zero to determine whether observed changes are irreversible. Ordinarily increments of pressure are eventually carried to a level causing rupture of the intestine before ending the experiment.

RESULTS

The normal intestinal wall shows roughly rectangular patterns of superficial serosal capillaries with intermittent flow, other vessels, varying in size, revealing a pulsating type of arterial flow or a steady current in the veins. It is instructive to observe the relationship of these vessels to each other during peristalsis: the vessels move back and forth with the motions of the intestinal wall, a situation very different from that seen in dead injected or dissected intestine. As peristalsis passes across any given area there is a "milking out" of the blood from the finer vascular elements, notably the venules and the capillaries; flow is immediately resumed after the peristaltic wave has passed by. The arteries are smaller in caliber than the veins of similar size, and they tend to be somewhat coiled in form, straightening out a bit with each systolic pulse. There is a greater velocity of flow within the arteries as compared with the veins of the same size. Arterial anastomoses across the antimesenteric border may easily be observed by moving the specimen about, demonstrating beyond any doubt the abundant intercommunication between the vessels of the intestinal wall.

The changes which take place on distention of the bowel are fairly constant. There is a rapid decrease in peristaltic activity, pressures of 10 to 15 mm. of mercury sufficing to produce a rather quiet wall in the loop being observed. There are progressive thinning of the intestinal wall and a decrease in the tortuosity of the vessels as distention increases. The blood flow itself shows a decrease in velocity according to a fairly standard pattern (Fig. 3). There is a uniform order in which the elements of the vasculature are interrupted, the first change being seen in the small venules and the next in the capillaries. Other elements begin to go out bit by bit as the higher pressures are reached. Cyanosis is readily observable on the venous side of the system, usually first apparent in the venules at about 30 to 40 mm. of mercury but extending later to include all the other radicles. At higher levels of pressure intermittent reversal of flow or to and fro oscillation develops in the cells packed within the larger vessels. Deflation of the intestine carried out after distention to 30 mm. or thereabout results in complete resumption of the normal flow

pattern, but when pressures are carried to higher levels, some capillaries fail to resume their function. Interstitial hemorrhages, once present, remain. Intravascular agglutination of cells begins to be apparent somewhere between 30 and 40 mm. of mercury pressure and is increasingly apparent from this point onward. It is our impression that this is evidence of local trauma to the intestinal wall or to the vessels within it produced by the distention. We have repeatedly passed from a loop showing marked intravascular agglutination to another loop in the same animal and found the latter to be free of it. This observation can be repeated

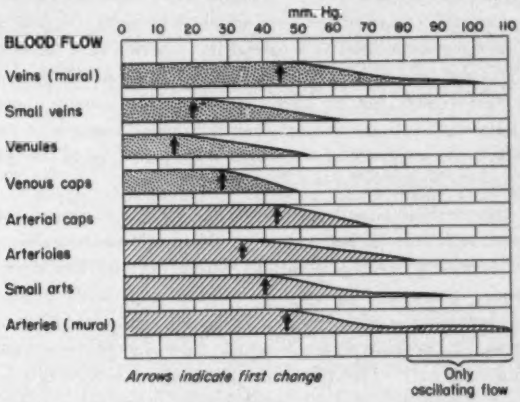

Fig. 3.—Summary of the effects of varying levels of distending pressure on the various vascular elements in the intestinal wall.

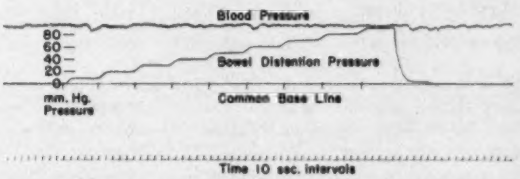

Fig. 4.—Photograph of tracings of a rabbit's carotid blood pressure taken during gradually increasing intraintestinal pressure (simultaneous tracings).

at will and is evidence that the process may be, and in the case of these experiments actually is, a local phenomenon.

To study a possible relationship between changes observed in the isolated loops and the systemic blood pressure, simultaneous tracings were made of the carotid blood pressure and the intraluminal pressure in 11 animals under experimental conditions exactly comparable to those used in the quarts rod experiments (Fig. 4). Intraenteric pressure in all 11 was carried to at least 80 mm. of mercury, and in five of the animals it was increased to the point of rupture of the gut, which usually takes place at about 120 mm. of mercury. No significant change in blood pressure was produced in nine of these animals. The other two showed transient drops in

pressure, varying between 20 and 30 mm. of mercury, not lasting more than 30 sec. and without direct relationship to intraenteric pressure change. Therefore it appears clear that the localized distention of the type utilized in these experiments does not produce any significant alterations in the systemic blood pressure of the animal. Conversely, systemic blood pressure changes do not appear to be a factor in the circulatory responses observed during distention in these experiments.

Observations are customarily continued to the point of intestinal rupture, which usually occurs in rabbits at between 100 and 120 mm. of mercury. At the higher levels of pressure deep cyanosis is seen in the veins, and interstitial hemorrhages become a pronounced feature of the area under observation. These appear first as small groups of red cells located as a rule at the junction of a branch with a larger vessel. We have not been able to observe the manner in which these red cells leave the lumen of their vessels, but we have noted that they usually appear in the area immediately adjacent to the vessel and then flow along the side of the vessel for a short distance to become pooled at some area within the wall of the intestine. They soon become grossly visible as large petechial spots.

All these observations have been carried out from the serosal side. Since the results are constant, it is our belief that they reflect fairly well the changes which take place, though there may well be situations within the villi which are not revealed by this technique. Studies which we have recently made of the villus circulation by means of cinephotomicrography from the mucosal aspect of the intestine lead us to hope that it may be possible to record some of the changes produced by distention on this circulation as well. The difficulties, however, of observing this aspect of the intestine during distention are much greater than those encountered with respect to the serosal side, and the problem has not yet been brought to a practical solution.

The effects of distention on the various elements of the intestinal circulation may be summarized as follows:

Pressure in Mm. Hg	EFFECTS
0-5	(This is considered to be normal.) Normal peristalsis is present, varying in degree with the elapsed time since feeding. There is rapid flow in the arteries and veins, without any evidence of clumping. Capillaries function in their normal intermittent manner.
15	There is moderate decrease in peristaltic activity. Slight slowing of the blood flow is seen in the venules, with return to a normal rate after deflation. Other circulatory elements reveal a normal rate and manner of flow.
20	Progressive slowing of flow occurs in the small veins and venules, which return to normal on deflation. Peristalsis has nearly ceased. There are thinning of the bowel wall and a decrease in tortuosity of the vessels (seen to a considerable degree in the dog whose vessels normally show great tortuosity).
30	Pronounced slowing is seen in the venules and small veins, with some decrease in rapidity of flow in the small arteries and arterioles as well. Many of the capillaries cease functioning, and some fail to regain their flow after deflation.
40	Blood within nearly all venous capillaries has ceased to flow, though arterial capillaries continue to function. Slowing of the blood now begins to appear in the larger arteries and veins. Reversal of flow appears in certain segments of vessels. Intravascular clumping begins to occur in both arteries and veins. Early cyanosis may be observed in the small veins.

50 Blood flow in the venules and small veins has almost stopped, and that within the small arteries is slowed. Arterial capillaries still flow through slowly. Venous capillaries have ceased to function. Cyanosis is marked on the venous side in all but the large mural trunks.

60 The blood in the larger arteries flows more slowly, and there is marked slowing and clumping of red cells in all of the larger veins and most of the arteries. There is notable cyanosis on the venous side, and some arteries reveal intermittent reversal of flow.

80 The blood in all vessels ceases to flow except the largest arteries and some of the larger veins, which show an oscillating type of to and fro motion of their contained cells. Interstitial extravasations of blood are abundantly apparent, and there is general blanching of the gut wall.

100 Interstitial hemorrhages become even more abundant and more pronounced in extent. Cyanosis is marked in all of the venous elements. Stagnation of blood in the capillaries has resulted in an impression of greater vascularity in that larger numbers can be visualized at the same time (in contrast to the normal situation, in which only part of them are functioning at any one observation). The blood supply of the wall is not well reestablished after distention to this degree. The bloody extravasations for the most part are not absorbed, and many capillaries remain plugged though flow in the larger vessels rather soon approximates its former rate.

120 At this degree of distention there is only occasional intermittent oscillating flow in the large arteries. The intestinal wall tears at about this degree of distention.

COMMENT

The quartz rod transillumination technique as described herein provides a practical means for studying the localized effects of acute intestinal distention on the circulation within the intestinal wall. The technique is an exacting one and demands meticulous attention to detail if physiological conditions are to be approximated during the course of the experiments. Nevertheless, repeated observations on many animals, with constant findings, indicate that the changes as described are those which regularly take place under these circumstances. The manner and the sequence of the interruption of flow appear sufficiently definite to justify the conclusions drawn.

It is recognized that the higher pressures used are considerably above those which most observers believe to be present in the obstructed human intestine. Further, since there is experimental data indicating that the human intestine ruptures only at much higher pressures than that of the rabbit, it may well be that even higher pressures would be required in man to produce the sequence of events herein described for the rabbit. Nevertheless, the similarity of the circulatory pattern makes it reasonable to suppose that the sequence of events and the manner in which the changes take place may well be the same in the human intestine as in the rabbit.

Of particular interest in connection with the problem of acute intestinal obstruction are the irreversible changes which take place. Since the rabbit intestine regularly shows irreversible changes after the higher levels of intraintestinal pressure one may reasonably assume that the same situation may occur in man. This would indicate that irreparable damage may be wrought by an attack of intestinal obstruction in which the distention becomes sufficiently severe. Undoubtedly recovery from the intestinal obstruction must carry with it a degree of ultimate revascularization to compensate for the permanent interruption of certain elements. Nevertheless, these

considerations add weight to the importance of early decompressive measures in all cases of ileus.

A final point which should be mentioned is the different reaction of the chronically distended intestine as compared with that seen in acute experiments. All surgeons are familiar with the fact that patients withstand repeated attacks of distention far better than they did their first one. Observations are now being made on animals subjected to chronic distention; while the data are not yet complete, it appears that the circulatory responses in chronically or recurrently distended intestine occur in a different manner, sequence and degree than in fresh acute nondistended loops of intestine. Further studies along these lines may help to explain the differences in the reaction of the individual to recurrent attacks of intestinal obstruction.

SUMMARY AND CONCLUSIONS

A practical technique for studying the circulation within the intestinal wall has been described.

Direct observation of the vessels in the intestinal wall of living animals reveals that there is demonstrable disturbance in circulation at pressures of 30 to 40 mm. of mercury, with nearly complete recovery after deflation.

Distending pressures of 50 mm. of mercury and higher produce irreversible changes in the mural circulation and in the intestinal wall; these include permanent interruption of many of the smaller vessels, interstitial hemorrhages and pronounced intravascular agglutination of cells.

The findings confirm previous observations on the harmful effects of severe acute intestinal distention. They lend weight to arguments for prompt and adequate decompressive measures in the treatment of all patients suffering from acute intestinal distention.

SURGICAL JAUNDICE IN INFANTS AND CHILDREN

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AND
JACK W. COLE, M.D.
CLEVELAND

THE PROBLEM of differentiating jaundice which is amenable to surgery from that which is not arises much less frequently in infants and children than in adults. The common causes of extrahepatic biliary obstruction in adults are very rare in children under 12 yr. of age. However, there are certain conditions which are peculiar to the younger age group that are frequently forgotten by those not working constantly with children.

We have studied 84 cases of jaundice in children under the age of 12 yr. seen in University Hospitals of Cleveland in the past 20 years. Tables 1 and 2 show the breakdown of these cases into surgical and medical groups.

The congenital hemolytic anemias with jaundice have been included in the surgical group because they are amenable to operative therapy. The so-called physiological jaundice of the newborn has been excluded, although most authors feel that this is not necessarily a physiological phenomenon. Waugh and his co-workers [1] pointed out that there was no correlation between degree of hemolysis and appearance of icterus neonatorum, and they reached the conclusion that the jaundice depended upon the functional ability of the liver cells to excrete the excess bilirubin. One hundred and seventy-five cases of erythroblastosis fetalis were not included, since making the clinical diagnosis is not so significant as formerly. Even before birth the possibility of an infant having the disease is now recognized by the finding of high titers of Rh-positive antibodies in an Rh-negative mother. However, some of the infants born of these mothers show no clinical evidence of erythroblastosis. Diamond, Allen, and Thomas [2] in a recent review have listed the indications for treatment of such infants.

The total number of cases in the medical group is small. We selected only those cases in which the jaundice was an outstanding feature of the disease. There were patients with various infections who exhibited a transient type of jaundice and these were not included in the series. There were also many with questionable histories of jaundice which could not be substantiated with laboratory procedures.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 24, 1951.

From the Department of Surgery, Western Reserve University School of Medicine, and University Hospitals of Cleveland.

1. Waugh, T. R.; Merchant, F. T., and Maughan, G. B.: Blood Studies on the Newborn, Am. J. M. Sc. **199**:9, 1940.

2. Diamond, L. K.; Allen, F. H., Jr., and Thomas, W. O.: Erythrobiastosis Fetalis, New England J. Med. **244**:39, 1951.

Some of the patients in the medical group presented diagnostic problems with respect to the type of liver disease present, but in only one instance was there any ambiguity as to whether the case was medical or surgical. This was a 9-mo.-old infant who had been jaundiced since birth. The bulk of the laboratory evidence pointed to an extrahepatic lesion. At the time of exploration normal cholangiograms were obtained, and liver biopsy revealed only bile stasis. Similar problems are not too unusual in adults, especially those with cholangiolytic hepatitis. It is often impossible to differentiate this hepatic disease from extrahepatic obstructions.

There is a period in children between the ages of 6 mo. and 12 yr. when the relative incidence of extrahepatic biliary obstruction is very low. In this study

TABLE 1.—*Nonsurgical Jaundice in Infants and Children*

Etiology	Cases		Age Incidence
	No.	%	
Infectious hepatitis	23	53	5 to 12 yr.
Sepsis	5	12	2 days to 3 mo.
Cirrhosis	5	12	3 mo. to 11 yr.
Homologous serum jaundice	2	5	10 mo. and 12 mo.
Banti's syndrome	2	5	4 yr. and 5 yr.
Toxic hepatitis	1	2	9 yr.
Sickle cell anemia	1	2	12 yr.
Lymphosarcoma	1	2	2½ yr.
Undetermined	3	7	.....
Total	43	100	

TABLE 2.—*Surgical Jaundice in Infants and Children*

Etiology	Cases		Age Incidence
	No.	%	
Congenital atresia of the biliary tract	25	61.0	1 day to 42 days
Congenital hemolytic anemia *	9	22.0	2 mo. to 10 yr.
Inspissated bile or mucous plug	3	7.3	1 day to 23 days
Inflammatory stricture of bile ducts *	2	4.9	2 yr. and 2½ yr.
Cystic dilatation of common duct	1	2.4	10 days
Duodenal diaphragm occluding ampulla	1	2.4	7 days
Total	41	100.0	

* Cholelithiasis present in one case.

we found only two cases of extrahepatic biliary obstruction in this age group, in contrast to 33 cases in the medical group. If the congenital hemolytic anemias with jaundice are added to the nonobstructive group, the ratio of incidence is about 1 to 20 in favor of the nonobstructive lesions. In a recent study made at the Los Angeles County Hospital by Bachhuber [3] of a series of 400 consecutive patients with jaundice, mainly adults, the ratio of obstructive to nonobstructive lesions was found to be approximately 1 to 1.

Congenital atresias of the biliary tract constitute the majority of cases in our surgical series. Ladd and Gross [4] give an excellent differential diagnosis of this

3. Bachhuber, C. A., and Gilbert, A. E.: Four Hundred Consecutive Cases of Jaundice, Am. J. Surg. **76**:144, 1948.

4. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941.

condition, to which may now be added the fact that erythroblastosis can be differentiated accurately by means of serological studies. Woolley [5] points out that hepatitis and cholangiolitis should be added to Ladd and Gross's differential diagnosis. Undoubtedly this is true, and probably many of the cases which we class as septicemia have associated impairment of liver function as the basis for jaundice. Here again, as in icterus neonatorum, studies indicate that there must be more reason for the jaundice than hemolysis alone. We do feel that septicemia and hepatitis in the newborn can offer the most difficulty in the differential diagnosis, but persistent studies for bile in the urine and stools will help to differentiate these from congenital biliary atresias. In addition, we agree with most authors that several weeks should pass before the decision to operate is made, as passage of time will help to rule out jaundice from other causes.

Inspissated bile and mucus in the bile ducts must be considered in the differential diagnosis of jaundice in the newborn period, but it is often impossible to diagnose this condition preoperatively. Two of the three patients with inspissated bile or mucous plugs had persistent and complete absence of bile in the gastrointestinal tract. They were given 25% solution of magnesium sulfate by tube, and both showed bile in the stools within 24 hr., and the jaundice rapidly subsided. The third infant died of an unusual kidney infection while waiting for surgery, and autopsy revealed the inspissated bile plug in the common duct. A fourth infant we felt had inspissated bile or mucous plugs in the common duct, because after irrigation of the ducts cholangiograms showed normal extrahepatic biliary passages. In spite of this, the child remained deeply jaundiced and eventually died. Autopsy revealed complete absence of the intrahepatic biliary ducts.

Study of our cases of biliary atresia revealed one interesting finding. All the infants with congenital atresia of the biliary tract have been of the white race. A review of the English literature fails to reveal a single proved case of biliary atresia in a Negro infant. In several case reports the race was not mentioned, but descriptions of the skin seemed to indicate that the infants were white. Although it cannot be said definitely that this condition does not occur in Negroes, it seems to be exceedingly rare. In contrast, all three patients with inspissated bile or mucous plugs producing jaundice were Negro infants. On the basis of these findings it would be wise to institute adequate cholagogue therapy before a Negro infant is subjected to an operation for congenital biliary atresia. This clinical finding is also a stimulus to the study of the racial distribution of other congenital anomalies.

Ladd and Gross [4] have reported that 20% of their cases of congenital biliary atresia could be benefited by surgery. We have not been so fortunate. In our series of 25 cases there was only one in which the extrahepatic biliary ducts could be anastomosed to the gastrointestinal tract.

There is little that can be added to the literature on congenital hemolytic icterus. Making the diagnosis of this disease is not difficult except in the very young. One patient, aged 2 mo., had a sibling with the disease, a fact that was of assistance in arriving at the correct diagnosis.

The only case of congenital cystic dilatation of the common duct in this series was unusual in that it was in a newborn infant with erythroblastosis. After replacement transfusions were given, the infant developed persistent vomiting and increas-

5. Woolley, P. U., Jr.: Clinical Conference, J. Pediat. **33**:509, 1948.

ing jaundice with no evidence of hemolysis. Exploration was performed because roentgenograms of the abdomen revealed a duodenal obstruction. The common duct presented a saccular dilatation, approximately 3 cm. in diameter, which was compressing the duodenum. After choledochoduodenostomy the jaundice and vomiting subsided. As Ladd and Gross [4] point out, it is unusual to find symptoms of this condition before the age of 6 mo., and the diagnosis is rarely made preoperatively simply because it is not considered. Shallow, Eger, and Wagner [6] give an excellent review of the etiology and diagnosis of congenital cystic dilatation of the common duct, and in their review of 175 cases they found that the preoperative diagnosis was made in only 8%. This condition should be strongly considered in the age group from 6 mo. to 12 yr. when the jaundice is of an obstructive nature.

An unusual cause of jaundice in this series occurred in a newborn with duodenal obstruction. Exploration of the duodenum revealed a double-leafed diaphragm with a normal ampulla of Vater situated between the two leaves. Removal of the diaphragms resulted in an uneventful recovery.

Cholelithiasis was found in two cases and was associated with other conditions. There were stones in the gallbladder in one of the cases of congenital hemolytic icterus, but they did not contribute to the jaundice. The other case was that of an inflammatory stricture, and here the stones probably contributed to the jaundice. Cholelithiasis in children is very rare and is usually associated with high blood levels of bile pigments or a previously severe infection.[7]

The two cases listed as inflammatory stricture are extremely interesting and raise certain etiologic possibilities. There is very little in the literature concerning common duct strictures, pancreatitis, or idiopathic hyperlipemia occurring in children. We feel from the studies of these two cases that there may be an association between these three conditions.

REPORT OF CASES

CASE 1.—I. B., a 2-yr.-old white girl, was admitted with the chief complaint of having been jaundiced since the age of 9 mo. The mother stated that the jaundice had fluctuated in intensity. There was no pain or vomiting associated with the jaundice. The child's birth had been normal, but she was never a good eater and gained weight poorly. Since the onset of her illness at the age of 9 mo., she had tended to have frequent loose bowel movements which were light in color. During the periods of increased jaundice the urine became quite dark. There was marked pruritus associated with the jaundice, and the mother said that the jaundice had become progressively worse during the three months preceding hospital admission. The child had also been troubled with a hacking nonproductive cough for about a year and a half prior to admission.

The family history revealed that one sister had died at the age of 9 mo. after an illness which consisted of respiratory stridor, convulsions, and terminal jaundice. A brother had been studied in the hospital because of symptoms suggestive of cystic fibrosis of the pancreas.

Physical examination showed a poorly developed and poorly nourished white child who was deeply jaundiced and had marked excoriations over the chest and arms. Temperature, pulse, and respirations were normal. The scleras were markedly icteric. The lungs were clear, and the heart was normal. The abdomen was slightly protuberant; however, there was no evidence of ascites or superficial venous distention. The liver was smooth, not tender, and palpable 6 cm. below the right costal margin. The spleen was palpable 4 cm. below the left costal margin. Neurological examination showed no significant abnormalities.

6. Shallow, T. A.; Eger, S. A., and Wagner, F. B.: Congenital Cystic Dilatation of the Common Duct, Ann. Surg. **117**:355, 1943.

7. Heringman, E. C., and Waiken, D.: Cholecystitis and Cholelithiasis in the Young, Am. J. Surg. **74**:27, 1947.

The erythrocytes numbered 3,450,000 and the leucocytes 6,300 per cu. mm. of blood. The urine was normal except for a 4+ positive reaction for bile, and no urobilinogen. The total plasma protein level was 5.75 gm. per 100 cc., with albumin 4.33 gm. per 100 cc. The icterus index was 150 units. The value for total cholesterol was 184 mg. and for cholesterol esters 65.5 mg. per 100 cc. of plasma. The serum alkaline phosphatase was 11.1 Bodansky units. The cephalin-cholesterol flocculation test reaction was negative, and the thymol turbidity reading was 0.6 units. The prothrombin time was 100% of normal, and erythrocyte fragility was normal. The total serum lipid was 710 mg. per 100 cc. Roentgenograms of the chest and upper gastrointestinal tract were not remarkable.

During the patient's first three weeks in the hospital, the icterus index fluctuated considerably, falling at times to 50 units, and during each fall the stools gave positive reactions for bile. On the 22d day an exploratory laparotomy was done. The gall bladder was not particularly distended and emptied with compression. The common duct was slightly dilated, and just proximal to the point where it passed behind the duodenum the duct was seemingly narrowed and compressed by large adjacent lymph nodes. There were many enlarged lymph nodes in the region of the hepatoduodenal ligament, some of them measuring 2 cm. in their greatest diameter. The common duct was opened, and a No. 5 ureteral catheter was passed easily into the duodenum. Unfortunately, no attempt was made to pass a larger instrument through the duct at this time. The ureteral catheter was left in the common duct, and the large lymph nodes impinging on the common duct were excised. Microscopic diagnosis of these nodes was endothelial hyperplasia. Postoperatively there was slight diminution in the degree of jaundice, and the stools were occasionally positive for bile. However, the icterus index remained at about 40 units, and the child continued to have marked pruritus. The common duct catheter was inadvertently removed on the 14th postoperative day before cholangiograms could be made. In view of the persistent jaundice, re-exploration was done on the 25th postoperative day. Cholangiograms performed on the operating table revealed that the common duct was markedly narrowed in the pancreatic portion and no contrast material would pass into the duodenum. A side-to-side cholecystoduodenostomy was performed at this time, and a catheter was left in the gall bladder for decompression. The postoperative course was uneventful, with a progressive fall in the icterus index. Subsequent cholangiograms through the cholecystostomy tube again revealed the common duct stricture, but dye passed readily into the duodenum through the anastomosis. The patient was discharged on her 66th hospital day.

Follow-up studies have shown no recurrence of jaundice; however, the patient continues to eat poorly and to have loose, foul-smelling stools. Duodenal tryptic activity is normal. The liver and spleen remain enlarged. Further metabolic studies are in progress.

CASE 2.—J. N., a 2½-yr.-old white girl, was entirely well until she was 1½-yr. old. At that time she had an attack of colicky pain in the right upper quadrant, accompanied with vomiting. She continued to have attacks of similar pain unrelated to meals for a few days, at which time it was noticed that her urine was dark, and obvious jaundice developed. She was hospitalized for four days, and the pain and jaundice subsided. Six weeks later she again had similar pain, and on this occasion she had fever though no jaundice appeared. This attack lasted three days. Four months later she had an attack similar to the first, and she was hospitalized for 17 days. She was well again for about four months, when the symptoms returned. This time the jaundice became progressively worse, and after six weeks of hospitalization she was transferred to University Hospitals. There was a history of clay-colored, greasy stools but no history of pruritus.

Physical examination revealed a well-developed, well-nourished girl who was markedly jaundiced. The abnormal findings were an enlarged, nontender liver extending 5 cm. below the right costal margin and a questionably palpable spleen. Roentgenograms of the chest, abdomen, and upper gastrointestinal tract were normal.

Laboratory studies revealed a hemoglobin content of 12 gm. per 100 cc. of blood. The leucocytes numbered 12,000 per 100 cc. of blood and the differential count was normal. The urine was strongly positive for bile and negative for urobilinogen. The total serum bilirubin level was 6.2 mg. per 100 cc., all of it giving a direct reaction. The alkaline phosphatase was 45.2 Bodansky units. The serum cholesterol was 417 mg. per 100 cc. and the cholesterol esters 173 mg. The total plasma protein level was 7.08 gm. and the albumin 5.17 gm. per 100 cc. The total

serum lipids were 2490 mg. per 100 cc. The cephalin-cholesterol flocculation test gave a negative reaction, and the erythrocyte fragility was normal. The Wassermann reaction was negative. Duodenal contents revealed diminished enzyme activity.

Exploration was done on the eighth hospital day. The liver was enlarged but otherwise appeared normal. The gall bladder and the common duct were markedly dilated, and there were many large lymph nodes in the region of the hepatoduodenal ligament, some of them measuring 2.5 cm. in their greatest diameter. One of these was definitely compressing the common duct just below the entrance of the cystic duct. The head of the pancreas was slightly enlarged and very firm. The common duct was opened and found to contain yellow bile and many small, soft stones. Probing the duct revealed that there was a constriction in the region of the pancreatic portion of the duct, and only the smallest Bakey dilator could be passed through into the duodenum. The duodenum was opened, and a normal ampulla of Vater was visualized. Choledochoduodenostomy was performed. A biopsy specimen was removed from the head of the pancreas, and a lymph node removed for examination.

The child had an uneventful postoperative course, and the icterus subsided rapidly. Cholangiograms through a cholecystostomy tube on the 10th postoperative day disclosed that the pancreatic portion of the common duct was markedly constricted but patent and that the anastomosis was also patent. Microscopic examination of the biopsy specimen showed normal pancreas, and the lymph nodes showed follicular hyperplasia.

The child has been followed now for 10 mo. and has been entirely asymptomatic.

COMMENT

There are notable similarities in these two cases. Both presented a marked narrowing of the pancreatic portion of the common duct and intermittent and fluctuating jaundice. The laboratory findings in both were indicative of extrahepatic obstruction. In both there was marked enlargement of the lymph nodes in the region of the hepatoduodenal ligament. Some of these nodes were as large as 2.5 cm. in diameter and were so situated that the common ducts were distorted. In the first case we were misled into believing that the obstruction was due to pressure from these lymph nodes, but reoperation proved we were wrong. In the second case we disregarded the lymph nodes, and examination of the common duct revealed the true nature of the obstruction. Both patients have had complete relief of the jaundice as a result of the bypassing procedures.

The pathogenesis of the common duct strictures in these two cases is purely a matter of conjecture. However, there is a certain amount of evidence which leads us to believe that chronic pancreatitis may be the etiological factor. That this occurs in adults is well-known, and Cole and his co-workers [8] in 1948 reported that in 10% of their cases of common duct strictures the condition was due to chronic fibrosing pancreatitis. It has not been reported, however, as occurring in children. The fact that the lesions are localized in the pancreatic portion of the duct suggests that they are due to inflammation in the pancreas. The marked lymph-node enlargement supports this assumption. In the first case we have no direct evidence for pancreatitis; however, both the preoperative and the postoperative courses have been those of severe metabolic disturbance very suggestive of pancreatic dysfunction, namely, anorexia, frequent foul-smelling and loose stools, and failure to gain weight. It is of interest that this child has a sibling who has been studied because of symptoms of cystic fibrosis of the pancreas.

8. Cole, W. H.; Reynolds, J. T., and Ireneus, C., Jr.: Strictures of the Common Dust, Ann. Surg. **128**:332, 1948.

In the second case there is the additional evidence of marked induration of the head of the pancreas. Biopsy of a specimen from the external surface of the gland failed to verify the impression of pancreatitis, as is so often the case.

A most interesting finding in this case is a fasting serum lipid value of 2,490 mg. per 100 cc., over three times the upper limit of normal. Thannhauser [9] called attention to the fact that hyperlipemia may occur in conjunction with chronic pancreatitis. A case of chronic relapsing pancreatitis in an 8-yr.-old boy has been reported by Collett and Kennedy.[10] These authors have also listed various other conditions in which hyperlipemia may occur in children, such as diabetes mellitus, nephrosis, blood dyscrasias, and marked hepatic disease. Lacking evidence for any of these diseases in this case, we feel that the hyperlipemia may possibly be interpreted as additional evidence of a chronic pancreatitis.

SUMMARY AND CONCLUSIONS

Eighty-four cases of jaundice in children are reviewed and grouped as to their various etiological factors. In general it may be said that there is an age period from 6 mo. to 12 or 15 yr. when surgical jaundice is relatively rare. The problem of differentiating medical from surgical jaundice, which is so difficult in adults, seldom arises in children.

We have not been able to find a case of congenital atresia of the biliary tract in a Negro infant in our series or in the literature, and we advocate adequate cholagogue therapy before a Negro infant is subjected to an operative procedure for this condition.

Two cases of common duct strictures are presented which we feel are due to chronic pancreatitis. Study of these cases leads us to two conclusions:

1. We should be very hesitant about ascribing common-duct obstruction to enlarged lymph nodes as a primary cause of jaundice.

2. Careful preoperative evaluation of pancreatic function should be made in children with obstructive jaundice, and the concept of pancreatitis as a cause of common-duct obstruction and jaundice should be kept in mind.

9. Thannhauser, S. J.: Hyperlipemia, in Christian, H. A., and MacKenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, Vol. 4.

10. Collett, R. W., and Kennedy, R. L. J.: Chronic Relapsing Pancreatitis Associated with Hyperlipemia in an 8 Year Old Boy, Proc. Staff Meet., Mayo Clin. **23**:158, 1948.

BILIARY TRACT DISEASE IN THE AGED

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MEDICAL care for the steadily increasing number of elderly persons becomes a greater problem each year. Definitive treatment is possible for more of the diseases of the aged, but their diminished reserve and decreased life expectancy cannot be disregarded in deciding on a therapeutic approach. A study of the dangers and results of treatment is therefore valuable.

Investigation of patients beyond the age of 70 who had been operated on in the past three years at the Denver General Hospital showed that biliary tract disease ranked next to carcinoma of the stomach and colon in mortality and next to repair of hernias in frequency (Table 1). The records of all elderly patients treated for biliary tract disease by operative or nonoperative means were therefore reviewed to evaluate further this disease and its response to different types of therapy.

The problems of geriatric surgery have received increasing attention, and the importance of biliary tract surgery has been recognized. There is ample autopsy evidence of the increased incidence of gallstones in elderly persons.[1] Glenn has recommended elective surgery for cholelithiasis at an earlier age, to prevent the complications which are so frequent and dangerous later in life.[2] Operative mortality rates of 11.7 to 16.6% have been reported for geriatric biliary surgery.[3] Quigley has pointed out the dangers of acute cholecystitis and jaundice [3b] and Welch the low mortality with elective operation.[3c] The necessity for greater precision and accuracy in all forms of treatment because of the decreased ability of elderly patients to withstand trauma or physiologic upsets has been emphasized.[4] Adequate evaluation and treatment of diminished cardiovascular or renal function and the replenishment of

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1. Rosenthal, J.: Gall-Bladder Disease in Elderly Patients, Ann. Int. Med. **20**:933, 1944.

2. Glenn, F.: The Surgical Treatment of Acute Cholecystitis in Patients 50 Years of Age and Over, Surg., Gynec. & Obst. **73**:649, 1941.

3. (*a*) Behrend, A.: The Treatment of Biliary Tract Diseases in Elderly Patients, Gastroenterology **8**:762, 1947. (*b*) Quigley, T. B.: Biliary Surgery in the Aged, New England J. Med. **221**:970, 1939. (*c*) Welch, C. S.: Surgery in the Aged, New England J. Med. **238**:821, 1948.

4. (*a*) Wilensky, A. O.: Preparation of Elderly Patients for Large-Scale Operations, New York J. Med. **47**:2432, 1947. Brooks, B.: Surgery in Patients of Advanced Age, Ann. Surg. **105**:481, 1937. Wangensteen, O. H.: Abdominal Surgery in Old Age, Lancet **64**:178, 1944.

depleted nutritional stores are also necessary.[5c] The dangers of emergency surgery have been shown by Cutler and by Beck,[6] while Guthrie and Niles [5a] have demonstrated the relative safety of operation after adequate preparation. An atraumatic surgical technique, a skilled anesthetist, and alert postoperative care are especially important.[7] The mortality associated with geriatric surgery has decreased, with cardiovascular and pulmonary disease now causing most of the deaths.[8]

PRESENT SERIES

Type of Case.—One hundred and three cases of biliary tract disease in patients over the age of 70 were studied in this series. The patients were treated in Denver General Hospital and Colorado General Hospital, according to a generally con-

TABLE 1.—*Surgical Mortality in 220 Patients Over 70*

Type	No. of Cases	Deaths
Carcinoma of stomach	14	5 (35.7%)
Carcinoma of colon	11	2 (18.2%)
Disease of biliary tract	29	5 (17.2%)
Hernia	77	4 (5.2%)
Benign rectal lesions	20	0
Carcinoma of breast	11	0
Peptic ulcer	16	0
Intestinal obstruction due to adhesions	9	0
Acute appendicitis	5	0
Acute diverticulitis	5	0
All others—single cases in each category	23	11 (47.8%)
Total	220	27 (12.2%)

TABLE 2.—*Hospital Mortality in 80 Cases of Disease of the Biliary Tract* *

	No. of Cases	Died	Per Cent
Operative	37	8	21.6
Nonoperative	43	11	25.6
Total	80	19	23.7

* The types of patients are not comparable (see text).

sistent plan of therapy, between January 1948 and October 1950. Their backgrounds were similar, and their treatment was usually supervised by both the medical and surgical services.

5. (*a*) Guthrie, D., and Niles, J. S., Jr.: Elective Surgery in the Aged, S. Clin. North America **28**:1341, 1948. (*b*) Ziffren, S. E.; Zager, L. L., and Cullen, S. C.: Hazards of Surgery Beyond the Age of 80, Geriatrics **5**:252, 1950. (*c*) Martin, J. D., Jr.: Surgical Risk in the Elderly Patient, Geriatrics **3**:296, 1948.

6. Cutler, C. W.: Urgent Surgery in the Aged, Ann. Surg. **126**:763, 1947. Beck, W. C.: Acute Abdominal Disease in the Aged, S. Clin. North America **28**:1361, 1948.

7. Bailey, F. W.: Surgery of the Aged, Am. J. Surg. **24**:487, 1934. Bancroft, F. W.: Surgery in the Aged, New York J. Med. **43**:37, 1943. Lundy, J. S.: Anesthesia and Supportive Therapy for Operations on Elderly Patients, Geriatrics **3**:361, 1948. Rovenstine, E. A.: Geriatric Anesthesia, Geriatrics **1**:46, 1946.

8. Evans, R. L., and Key, S. N.: Surgery in the Aged, Pennsylvania M. J. **45**:818, 1942. Carp, L.: Basic Principals in Geriatric Surgery, Ann. Surg. **123**:1101, 1946. Waters, W., and Snell, A. M.: Diseases of the Gall Bladder and Bile Ducts, Philadelphia, W. B. Saunders Co., 1940. Welch.[5c] Wilensky.[4a] Martin.[5c]

The number, but not the type, of diseases treated by operation and by nonoperative means was comparable, and the mortality of each was approximately the same (Table 2). The series of 103 cases includes 23 in which the diagnosis of biliary tract disease was made incidentally at operation or autopsy and which are included only in calculations of the mean age and sex of the group. It is interesting, however, to note so many cases in which biliary tract disease was present but was asymptomatic or secondary to other complaints.

The mean age of the patients was 77.1 yr., with the oldest 92 yr., and no significant age difference existed between those treated surgically and those treated nonsurgically. Twenty patients were over the age of 80, and two patients, both of whom were operated on, were over 90. The surgical mortality rate for patients over the age of 80 was 50%, while the nonsurgical mortality rate in this age group was only 20%. There were 56 men and 47 women, an unexpected masculine predominance.

Type of Biliary Tract Disease.—Of the 80 patients treated primarily for biliary tract disease, 75% had gallstones (Table 3). Cholelithiasis and its complications

TABLE 3.—*Primary Pathologic Diagnosis*

Disease	Surgical	Nonsurgical	Total	Mortality
Uncomplicated cholelithiasis	17 (5.8%)	11 (18.1%)	28	(10.7%)
Complications of cholelithiasis				
Cholecystoduodenal fistula	1 0	0	1	
Cholangitis, suppurative	0	4 (100%)	4	(100%)
Empyema	1 (100%)	1 (100%)	2	(100%)
Perforation with abscess	2 (50%)	1 (100%)	3	(66.6%)
Perforation with generalized peritonitis	2 (50%)	0	2	(50%)
Choledocholithiasis	12 (33.3%)	7 (14.2%)	19	(26.3%)
Liver abscess	0	1 (100%)	1	(100%)
Total	18 (38.8%)	14 (57.0%)	32	(46.8%)
Other Diseases—no stones				
Acute cholecystitis	0	10	10	0%
Chronic cholecystitis	1	7	8	0%
Torsion of gallbladder	1	0	1	0%
Stenosis of common duct	0	1 (100%)	1	100%
Total	2	18	20	5%

accounted for 94.5% of the surgical cases and all of the deaths in the surgical group. More than half of the patients with gallstones also presented some complication of this disease, and the mortality rate among those with complicated cholelithiasis was 56.8%. Choledocholithiasis was the most frequent complication, but suppurative biliary tract diseases carried by far the highest mortality. Not included were two cases of carcinoma of the gallbladder, in both of which there were stones, with 100% mortality.

The four patients with acute suppurative cholangitis were treated nonsurgically, and all died. It is of interest that three were admitted with the diagnosis of pneumonia, two showed no indication of jaundice, and in none was the correct diagnosis made prior to autopsy. One of these also had a pericholecystic abscess and liver abscesses, and another had extensive hepatic necrosis at autopsy. All showed a progressive febrile illness, with poor localizing signs.

It is especially noteworthy that of 60 patients with cholelithiasis, six, or 10%, showed evidence of perforation, three with generalized peritonitis, two with pericholecystic abscess and one with a cholecystic duodenal fistula. This represents an increase in the incidence of perforation when a comparison is made with younger age groups.

Most of the patients with cholecystitis without cholelithiasis were treated nonsurgically, and no deaths occurred. The clinical diagnoses in this group were usually confirmed by cholecystography. It is likely that gallstones were present in some of these but remained undiscovered.

The majority showed more than one type of biliary tract disease. Cholelithiasis was usually accompanied with cholecystitis, and several of the suppurative complications of cholelithiasis often occurred in one person. Thus, there were actually more types of biliary tract disease than is indicated in Table 3, since only the primary disease process of each case was listed. Marked hepatic damage was not a notable feature, with the diagnosis of biliary cirrhosis being made only three times.

Diagnostic Features.—Pain was the primary symptom in over 90% of the cases, while nausea and vomiting occurrred in less than half. Jaundice was present in one-third, with an associated mortality of 37%. Constipation was a frequent complaint, with a history of food intolerance, fever, or weight loss rarely obtained.

Abdominal tenderness was noted in only 60% and muscle spasm in only 20% of the acute cases. Liver enlargement was found more frequently than a palpable gallbladder.

The white blood cell count in the acute cases averaged 17,500 and rose to an average of 20,600 in those operated on as an emergency. Temperature elevations generally corresponded to the degree of elevation of the white blood cell count.

Incorrect diagnoses on the patients' admission were made in 12.5% of the cases. Three were admitted with the diagnosis of pneumonia, and three were thought to have had a cerebral vascular accident because of their almost moribund condition. In two cases a diagnosis of peptic ulcer was made and in one each a mistaken diagnosis of acute appendicitis, angina pectoris, intestinal obstruction and perforated duodenal ulcer. In view of the generally poor reliability of the physical findings, it is surprising that more incorrect diagnoses were not made.

Associated Diseases.—The degenerative diseases of old age were frequently encountered, complicating the biliary tract disease and increasing the mortality. Arteriosclerotic heart disease was the commonest, occurring in over one-fourth of the patients and associated with a mortality rate of almost 40%. Hypertension and hypertensive cardiovascular disease were much less frequent and the associated mortality was lower. Severe generalized arteriosclerosis and recent cerebral vascular accidents carried a high mortality, as did pyelonephritis. Osteoarthritis was more frequent but was associated with no increase in mortality. Abdominal carcinomatosis was found in four patients, all of whom died.

The recognition and treatment of these associated diseases offers one of the main hopes for reducing the mortality of any surgical procedure in elderly persons. Not only must the extent of the diseases be considered in determining whether the patient can withstand operation, but their effect on the patient's life expectancy and future course should be estimated before an elective operation is performed. The chronological age of the patient is less important than the extent of the associated disease in making such a decision.

Treatment in Acute and Chronic Cases.—Most of the patients in this series were admitted with acute disease of the biliary tract. The average duration of acute symptoms was nine days, allowing considerable progression of the disease before hospitalization. About one-fourth of the patients with an acute condition were operated on as an emergency, with a mortality of 41.6% (Table 4). Those cases in which elective operation could be deferred until a later date showed a much lower mortality. Patients who were not operated on also had a lower mortality rate.

Patients who were admitted with chronic disease of the biliary tract gave a history of having had symptoms for an average of eight and a half years, many of them having been previously denied operation because of their age. The surgical mortality in this group was only 6.2%.

The nonemergent operative treatment of acute biliary tract disease is thus safer, unless progression of the disease makes operation mandatory. Elective surgery, carried out when the disease is quiescent and there is time to prepare the patient for operation, results in the lowest mortality rate.

Preoperative Care.—Patients admitted during an acute attack were usually treated with antibiotics and antispasmodics, sedation, intravenous injections of

TABLE 4.—*A Comparison of the Mortality in Acute and Chronic Cases, With and Without Operation*

	Number	Mortality
Acute cases, emergency operation	12	5 (41.6%)
Acute cases, elective operation	9	2 (22.1%)
Acute cases, without operation	30	8 (26.6%)
Chronic cases, with operation	16	1 (6.2%)
Chronic cases, without operation	13	3 (23.1%)*
Total	80	19 (23.7%)

* Two of these were cases of carcinoma of the gallbladder.

fluid, and gastric suction. Further preoperative care was seldom possible when emergency operation was necessary. In most instances the acute attack subsided rapidly, and all of these measures except antibiotic therapy were discontinued. Associated diseases were then investigated and treated, and metabolic deficiencies were corrected. Any site of infection was treated and the patients mobilized and accustomed to hospital routine. Blood transfusions were frequently given for anemias and hypoproteinemia. The benefits of such treatment were readily apparent in the operative and postoperative periods.

No single clinical or laboratory test was found to be of outstanding value in determining the ability of the patient to withstand operation. Obesity, angina pectoris, and albuminuria were associated with no increase in mortality. The most valuable tests of liver function were thought to be the prothrombin time and cephalin flocculation determination.

Operative Procedures.—Cholecystectomy was the most frequently performed operation and showed a low mortality rate (Table 5). There was one death in the five cases in which it was performed as an emergency procedure, but only one death occurred in the 20 cases in which elective operation was possible. Choledochostomy was performed with cholecystectomy in 12 elective cases, and none of the patients died. There was one fatality, however, among the four patients treated

solely by choledochostomy. The high mortality associated with cholecystostomy in this series was probably due to its use as an emergency procedure and reflects the dangers of having to operate for an acute condition in an unprepared patient rather than any fault in the procedure itself. Elective cholecystectomy, with choledochostomy if necessary, was thus found to be both effective and safe in this age group.

Postoperative Care.—In addition to continuing the supportive measures of the preoperative period, especial care was taken to prevent pulmonary and thrombotic complications postoperatively. Early mobilization, antibiotic therapy, and minimal sedation were emphasized. Patients were encouraged to cough and to resume eating as soon as possible and were frequently examined for evidence of thrombophlebitis or of pulmonary infection.

Postoperative Complications.—Despite the precautions taken, 16 of the 37 patients operated on had postoperative complications, and eight of these died. Bronchopneumonia was the commonest complication, occurring in five cases, with four deaths. In two patients wound infections developed and there were two patients with wound disruption, but none of these died. Disorientation and hyperpyrexia were often associated with the infectious complications and carried a high mortality.

TABLE 5.—*Operative Procedures in Thirty-Seven Cases* *

Operation	Emergency		Elective		Total	
	Lived	Died	Lived	Died	Lived	Died
Cholecystectomy	4	1	19	1	23	2 (8.0%)
Choledochostomy	0	0	15	1	15	1 (6.2%)
Cholecystostomy	3	4	0	0	3	4 (57.1%)
Total	7	5	34	2	41	7 (17.0%)

* There were 48 procedures in the 37 cases. This table represents, therefore, a comparison of the various types of common surgical operations on the biliary tract and the associated mortality with special reference to whether they were emergency or elective. There was no mortality in the group in which more than one procedure was performed.

Persistent biliary drainage, atelectasis, and melena were each observed in one patient, and all of these died. There was no mortality associated with pneumonitis, a temporary common duct obstruction, and a cerebral vascular accident, which occurred in one case each. Infectious complications thus were the most frequent and dangerous, despite antibiotic therapy.

Postoperative Deaths.—A striking predominance of pulmonary causes of death was found (Table 6). Infection, emphysema, and retained bronchial secretions were responsible for these. Only one patient died of heart failure and one of embolic disease. None died of complications at the operative site. Most of these patients had several disease processes contributing to their debility, and the primary cause of death was often difficult to determine. Cardiovascular, renal, and hepatic diseases were frequently found, and peritonitis was noted twice, but none of these were considered to have actually caused the patient's death. Autopsies were obtained in seven of the eight deaths.

These patients lived an average of 11.6 days after operation but usually responded poorly throughout the postoperative period. Five of the eight had emergency operations, and seven had complications of cholelithiasis. The three sudden deaths occurred around the seventh postoperative day. Adequate time for

intensive treatment was available for the other five patients, and their lack of response indicates inadequate preoperative care.

Mortality in Nonoperative Cases.—Nonoperative therapy closely followed the regimen of preoperative care previously described, except that the associated disease processes were generally severer and required especial attention. These patients stayed in the hospital an average of 15.2 days, however, compared with 31.4 days for patients who were operated on.

Every death in this group was due primarily to the patient's biliary tract disease, and most of them could be attributed to one of the complications of cholelithiasis (Table 6). The most frequent cause of death was acute suppurative cholangitis, which was discussed previously. The only patients whose deaths could not be attributed directly to gallstones were those who died of carcinoma of the gallbladder and of stenosis of the common bile duct. These deaths occurred after an average hospital stay of 14.9 days.

TABLE 6.—*Primary Cause of Death*

Surgical	
Bronchopneumonia	4
Spontaneous pneumothorax	1
Pulmonary embolism	1
Massive collapse of both lungs	1
Arteriosclerotic heart disease	1
Total	8
Nonsurgical	
Suppurative cholangitis	4
Choledocholithiasis	2
Carcinoma of gallbladder with metastases	2
Liver abscess	1
Acute pancreatitis	1
Stenosis of common bile duct with cirrhosis of liver	1
Total	11

As with those who died after operation, most of these patients had several disease processes which contributed to their deaths. Their primary diseases, however, were due to gallstones, and their deaths might have been prevented had these been removed before complicated biliary tract disease resulted.

Follow-up Observations.—Of the 61 patients who left the hospital, 44 were contacted by letter or telephone in December 1950. Seven of these were found to have died. Three of the seven were patients who had been operated on, and all had had gallstones at the time of operation. Although no severe associated diseases had been found in these patients, they lived an average of only four months after leaving the hospital. The four deaths in patients who had been treated without surgery occurred an average of nine months after discharge from the hospital. For all these patients a diagnosis of acute cholecystitis without cholelithiasis had been made, and they had responded well to treatment in the hospital. Three of them also had arteriosclerotic heart disease. Those who died were no older than the mean age of the group.

Follow-up reports of 20 living patients who had been treated surgically showed 16 to be improved and four unimproved. Only one of the unimproved patients had definitely had further attacks, and this was a patient with a congenitally absent

gallbladder who had had stones removed from the common duct. Each of the other three patients had undergone an elective cholecystectomy for chronic cholecystitis, two also having cholelithiasis. There is no apparent reason for the poor results in these cases. Follow-up periods ranged from 3 to 36 mo., with a mean of 16.6 mo.

Seventeen living patients who had been treated nonsurgically were followed up, and 13 of these considered themselves to be improved. Three of the improved patients were continuing to have attacks of pain, however, and one was jaundiced. All of the four patients who were unimproved were continuing to have attacks of pain. Two of these had been treated for chronic cholecystitis and two for acute cholecystitis, but none had demonstrable stones. They had not responded as readily to treatment in the hospital as the rest of the group. Follow-up periods in this group ranged from 10 to 33 mo., with a mean of 19.5 mo.

According to the patients' opinions, the number who were improved is about the same in both surgical and nonsurgical groups. Only one patient in the surgical group was continuing to have definite symptoms of biliary tract disease, however, while eight patients in the nonsurgical group were continuing to have such symptoms.

SUMMARY

With the increasing number of elderly persons, further information about their disease processes and response to present therapy is of value. The frequency and high mortality of biliary tract disease in the aged especially warrant investigation.

Previous reports of this disease emphasize the increased incidence of gallstones and their complications in the aged, the dangers of jaundice, and the high mortality associated with emergency operation. Important features in the surgical management of the elderly patient have been pointed out by many.

This series of 103 cases of biliary tract disease in patients over the age of 70 showed little difference in mortality between those treated surgically and those treated nonsurgically. However, the patients with uncomplicated conditions without stones were largely treated medically while those with calculus or with complicated conditions were treated surgically. Surgical mortality rose significantly in patients over the age of 80. There was an unexpected predominance of males in the series. Cholelithiasis occurred in most of the cases and often caused other complications, which showed a high mortality. Physical findings were generally of little diagnostic value, with incorrect admission diagnoses made in a number of cases. The degenerative diseases of old age were frequently found and were associated with increased mortality. Emergency operations carried a high mortality rate, while that of elective procedures was low. The incidence of perforation of the gallbladder, however, was greater than that found in younger age groups.

Cholecystectomy was the most frequently performed operative procedure, with a low mortality rate. Choledochostomy, with elective cholecystectomy, caused no deaths. Cholecystostomy was performed only as an emergency procedure, with a high mortality rate. Preoperative and postoperative care were stressed, but the incidence of complications was high. Pulmonary infections were the most frequent and dangerous and accounted for most of the surgical deaths. Cardiovascular and embolic disease each caused only one death. Deaths in the patients treated without operation were all due primarily to biliary tract disease, usually a complication of cholelithiasis. In several of these the condition was not recognized until autopsy.

Follow-up showed a similar mortality in surgical and nonsurgical groups. Most patients in both groups were generally improved, but a far greater number in the nonsurgical group were continuing to have symptoms of the disease.

CONCLUSIONS

1. Biliary tract disease in the aged is frequent and dangerous.

2. The incidence of cholelithiasis increases with age and also the ratio of involvement of men to women.

3. The complications of cholelithiasis cause most of the deaths from biliary tract disease in this age group.

4. Emergency operation carries a high mortality and should be avoided if possible, yet the increased incidence of perforation emphasizes the need for the consideration of emergency treatment in the presence of acute cholecystitis.

5. Elective cholecystectomy, with choledochostomy if necessary, is well tolerated by elderly persons and should be performed during a quiescent period of the disease to prevent further acute attacks and the dangerous complications of cholelithiasis.

6. Nonsurgical management is preferable when other disease processes render surgery unduly dangerous or make the future of the patient too uncertain.

7. Postoperative complications, especially pulmonary infections, are more frequent and dangerous in this age group. Adequate preoperative and postoperative care is necessary to lower the mortality from this source.

8. Elderly patients are generally improved by either surgical or nonsurgical treatment, but those treated surgically enjoy a far greater freedom from continued symptoms and dangers of biliary tract disease.

LOCALIZATION OF RADIOACTIVITY OF COLLOIDAL GOLD[198]

A Preliminary Report

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ONE OF THE shortcomings of the therapeutic use of radioactive isotopes has been failure of specific localization of activity. Iodine[131] is specific for functioning thyroid tissue, but none of the other isotopes has been as specific in its localizing abilities. Phosphorus[32] has some affinity for the hematopoietic system and has been used for treatment of certain blood diseases. Gallium has some specificity for bone and has been used for the treatment of bone tumors. Localization of most isotopes has not been as specific as was hoped. In the following work an effort was made to localize radioactivity by local implantation rather than by specific tissue affinity. Work was done on dogs, and the routes used were intra-arterial, intravenous, intraperitoneal, intrapleural, and intravesicular. The results are promising enough to warrant presentation of this preliminary report. Colloidal gold[198] has been used before, mostly by Paul Hahn and his associates,[1] and has been found to have some affinity for the reticuloendothelial system when given intravenously. Gold[198] is a readily available, very pure isotope, easily prepared and relatively nontoxic.[2]

PREPARATION OF THE ISOTOPE

Gold[197] was activated to gold[198] at the pile at Oak Ridge. It was sent to the Abbott Research Laboratory in Chicago, where (under the supervision of Dr. D. L. Taburn) it was put in a colloidal solution. The particles of the colloid ranged between 0.003 and 0.004 μ. Concentration was approximately 200 mc. per 12 to 13 cc., representing 54 mg. of metallic gold. The solution could be sterilized repeatedly by autoclaving without affecting its activity. After the gold was put into the colloidal state it was flown to Oak Ridge.

Gold[198] is primarily a beta emitter, emitting negative electrons with a maximum energy of 0.97 mev and gamma rays with energy of 0.44 mev. The gamma rays allow external counting to be done with some degree of accuracy, but beta rays are

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From the Department of Surgery, University of Louisville School of Medicine and the Oak Ridge Institute of Nuclear Studies, Medical Division.

1. Hahn, P. F., and Sheppard, C. W.: Ann. Int. Med. **28**:598, 1948.

2. R. Arnold Griswold, University of Louisville School of Medicine, suggested this approach in the use of radio-activity. The work was done under the close supervision of Dr. Marshall Brucer, Head of the Medical Division of Oak Ridge Institute of Nuclear Studies. Dr. Don Rathbun, of the University of Texas School of Medicine, contributed technical help and advice.

the primary therapeutic rays of this isotope. Fifty per cent of the beta particles in gold travel about 0.38 mm. in tissue; thus, the activity is localized to the immediate area. The half-life is 2.73 days, and 75% of the radiation is delivered in 5.5 days.

TOXICITY

Toxicity studies on stable gold have been worked out with sufficient accuracy and clinical experience. Little work has been done on the toxicity of colloidal gold. It is thought, because of the nature of the colloidal preparations, that the toxicity of colloidal gold is probably lower per milligram than that of gold salt.

METHOD OF CALIBRATION

The solution was calibrated by comparing with a radium standard using a Lauritsen electroscope. The formula used was div/min/mg.Ra = div/min/mc. $Au^{198} \times \frac{8.4}{2.4}$.[3]

METHOD OF ADMINISTRATION

Dogs were employed as the experimental subjects. Five millicuries were used in each injection, which was made with a 2 cc. syringe protected with a thin covering of metallic lead. This protection was not sufficient to eliminate all radiation hazard, but hazard was minimized by quick work.

AUTOPSY AND ASSAY

After each injection, autopsy was performed at approximately one-half-life of gold, which was 2.7 days. The organs were weighed in their entirety, and a sample was taken, weighed, digested in nitric acid and papain, and brought up to a total of 10 cc. in a volumetric flask. The activity in this wet sample was measured in a Geiger end-tube counter. Standard samples from the original solution were run daily to check the decay curve and compare with autopsy readings. In the calibration of activity, the right kidney was used as unity, and all figures in the charts are in proportion to this kidney. All organs are compared with the kidney of the same animal. All surgical procedures were done under sterile conditions. In addition to assay for radioactivity, specimens were taken for histological studies. Reports from the pathologist, Dr. Don Rehbock, showed no direct evidence of damage to the various organs from this amount of radioactivity.

INTRAVENOUS INJECTION OF COLLOIDAL GOLD

Table 1 shows distribution of radioactivity following intravenous injection in five dogs, the saphenous vein being used in four and the internal jugular vein in the other. Distribution was not unlike that found by other investigators,[4] with primary localization in liver and spleen, and a lesser amount in ribs, mesenteric lymph nodes, kidney and lungs. Other organs had little uptake. The liver took up well over 90% in many of the dogs.

ARTERIAL INJECTIONS

1. *Renal Artery.*—When the isotope was injected into the renal artery, with no occlusion of the renal vein, the distribution of radioactivity was almost identical to that with intravenous injection (Table 2). When, after injection into the renal

3. Marrinelli, L. D.; Quinby, E. H., and Hines, G. J.: Am. J. Roentgenol. **59**:260, 1948.
4. Hahn, P. F., and others: J. Lab. & Clin. Med. **32**:1442, 1947.

artery, the artery and vein were both occluded for one minute, distribution was entirely different. The kidney that received the injection had 20 to 25 times more activity than the opposite kidney, and the distribution in other organs was usually much lower than after intravenous injection. Radioautograms taken from the

TABLE 1.—*Intravenous Injections of Approximately 5 Mc. of Colloidal Gold*[198] *

Dog No.	15	5	14	10	28
Code No.	020034	020036	020033	020038	020042
	Intravenous Injection, Vein				
	Saphenous 1 per Week for 3 Wk.	Saphenous	Saphenous	Internal Jugular	Saphenous
Right kidney	1.0	1.0	1.0	1.0	1.0
Left kidney	4.9	2.1	0.7	0.5	0.3
Liver	287.0	13.0	116.3	196.0	150.0
Spleen	20.2	36.0	43.2	19.9	14.1
Pancreas	0.2	0.2	1.3	0.5	0.3
Lungs	1.7	1.0	4.1	0.4	0.6
Bladder	0.1	0.1	0.2	0.1	I †
Heart	1.3	...	I †	0	0.1
Peritoneum	0.6	...	...	...	...
Diaphragm	0.2	...	...	...	...
Mesenteric lymph node	2.2	...	0.84	0.3	0.2
Muscle—Hindleg	0.1	I †	...	I †	...
Foreleg	...	I †	...	...	...
Bone —Hindleg	1.3	0.1	...	I †	...
Foreleg	...	0.1	...	...	...
Rib	4.3	...	3.9	...	0.4
Pleura—Parietal	...	...	...	...	1.7
Visceral	...	...	...	...	2.5
Stomach	...	...	...	...	0.1
Small intestine	...	...	...	...	0.1
Large intestine	...	...	...	...	0.1

* Showing values of activity in organs, per gram weights, corrected for decay and in ratio to right kidney. Autopsy was performed 2.7 days after injection.
† Uptake was infinitesimal.

TABLE 2.—*Injections of Approximately 5 Mc. of Colloidal Gold*[198] *in Left Renal Artery**

Dog No.	4	2	3	1	23
Code No.	020023	020021	020022	020020	020042
		Renal Artery			
	Renal Artery No Occlusion	Occlusion of Artery and Vein for One Minute			Intravenous Injection
Right kidney	1.0	1.0	1.0	1.0	1.0
Left kidney	1.9	24.4	15.4	32.2	0.3
Liver	113.4	4.4	173.2	4.7	150.0
Spleen	14.9	0.7	30.9	10.7	14.1
Pancreas	0.6	0.4	0.2	3.6	0.3
Bladder	0.1	I †	0.5	0.9	I

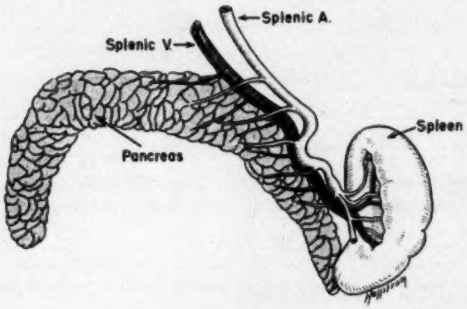
* See footnote to Table 1.
† Infinitesimal.

injected kidney showed that distribution was fairly diffuse, being present in the medulla and cortex in equal amounts.

2. *Splenic Artery.*—The splenic artery in the dog supplies the distal half of the pancreas as well as the spleen (Fig.). Efforts at localization in the pancreas were made by injection into the splenic artery. Splenectomy was performed prior to injection to avoid localization in the spleen. When injection was made into the

proximal splenic artery as it approaches the pancreas, concentrations several thousand times those following intravenous injection were found in the head, body and tail of the pancreas (Table 3). When the injection was made more distally in the artery the concentration was more distal in the pancreas. In all these experiments artery and vein were occluded for one minute after the injection.

3. *Femoral Artery.*—Attempts were made to localize activity in an extremity by injection of the major vessels. When the femoral artery was used (Table 4) without occlusion of the artery and vein, there was no particular localization. When the vein and artery were occluded, there was still no significant change, nor did injection into the lumbar aorta give significant localization. In Dog 7 a tight tourniquet was placed on the hindleg for five minutes after injection in an effort to prevent activity from entering this extremity. However, the autopsy findings were not unlike those with other arterial injections.



Splenic artery distribution to pancreas and spleen of dog.

TABLE 3.—*Injections of Approximately 5 Mc. of Colloidal Gold*^{198} *into Splenic Artery and Vein**

Dog No.	13	16	17	18	15
Code No.	020032	020035	020036	020037	020034
		Splenic Artery (After Splenectomy) Occlusion of Splenic artery and Vein for One Minute			
	Splenic Vein	Injection Near Head	Body	Body	Intravenous Injection of Saphenous Vein
Right kidney	1.0	1.0	1.0	1.0	1.0
Left kidney	0.7	1.1	0.6	0	4.9
Liver—Midlobe	129.9	44.4	19.8	28.6	287.0
Left lobe	133.1	...	...	...	...
Right lobe	179.2	...	...	...	...
Spleen	7.5	...	...	...	20.4
Pancreas—Head	...	509.2	1.6	18.0	...
Body	0.1	1,590.1	0.7	0.7	0.2
Tail	...	18.57	17.4	118.0	...
Bladder	0.5	0.6	0.5	0	0.1
Mesenteric node	0.1	3.6	0.4	0	2.2
Heart	...	3.5	0.1	0.1	1.7
Lungs	0.6	0.6	0.2	0	1.7
Muscle—Leg	0.2	1.3	0.2	1.7	0.1
Bone—Leg	0.1	2.6	0.1	0.1	1.3

* See footnote to Table 1.

TABLE 4.—*Arterial Injections of Approximately 5 Mc. of Colloidal Gold*[198] *

Dog No.	9	8	10	11	6	7	15
Code No.	020028	020027	020029	020030	020024	020025	020034
	Femoral Artery (Left)		Lumbar Aorta		Blind Injection		
	No Occlusion	One-Minute Occlusion of Femoral Vein	Operative Exposure			Tourniquet on Right Hindleg, 5 Min.	Intravenous (Saphenous Vein)
Right kidney	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Left kidney	1.2	1.0	1.2	1.2	4.1	0.7	4.9
Liver	190.8	167.4	12.4	164.6	10.9	3.1	287.0
Spleen	28.4	0.9	1.0	6.4	2.0	0.5	20.2
Pancreas	0.5	0.4	0.2	0.2	0	0.1	0.2
Mesenteric node	...	...	...	0.2	5.5	0.1	2.2
Bladder	0.3	0.3	0.1	0	0.6	I †	0.1
Lungs	...	...	0.4	0.4	3.0	I	1.7
Muscle—Hindleg, right	0.1	0.1	0.1	...	...	I	0.1
Hindleg, left	I	I	...	I	0	0.1	...
Foreleg	I	I	0.1	0.1	0	0.1	1.3
Bone—Hindleg, right	0.1	I	0.2	...	0	0	...
Hindleg, left	0.4	0.2	...	0.7	0	0	...
Foreleg	0.0	I	I	1.1	0	5.9	...

* See footnote to Table 1.
† Infinitesimal.

TABLE 5.—*Injections into Pleural Cavity of Approximately 5 Mc. of Colloidal Gold*[198] *

Dog No.	20	21	19
Code No.	020039	020040	020038
	Pleural Space (Right)		Intravenous (Internal Jugular Vein)
Right kidney	1.0	1.0	1.0
Left kidney	1.6	0.8	0.5
Liver	105.1	39.6	196.0
Spleen	12.8	9.7	19.9
Pancreas	I †	0.6	0.5
Bladder	I	0.7	0.1
Mesenteric node	0.2	1.3	0.2
Heart	0.5	0.1	0
Right lung			
Periphery	24.2	6.5	0.4
Midlung	6.9	6.9	0.4
Hilus	15.6	4.7	0.3
Pleura			
Visceral	...	64.0	...
Parietal	...	612.8	...
Left lung			
Periphery	5.4	22.9	...
Midlung	2.3	0.8	...
Hilus	2.1	6.4	...
Pleura			
Visceral	...	26.9	...
Parietal	...	24.5	...
Rib	9.3	4.4	...

* See footnote to Table 1.
† Infinitesimal.

PLEURAL INJECTION

Efforts to localize activity in the pleura were made in two dogs. Approximately 5 mc. of colloidal gold[198] was injected into the pleura on the right side. At autopsy there was localization in this pleural space several thousand times that in the intravenous control experiment. As shown in Table 5, activity was present primarily in visceral and parietal pleuras. However, the midportion and the hilus of the lung also had increased activity.

PERITONEAL INJECTION

The peritoneal cavity in three dogs was injected with 5 mc. of gold. At autopsy there was a much higher concentration of radioactivity in the peritoneum than in the intravenous control experiments (Table 6). Primary localization in the peritoneal cavity was in the omentum, which had an extremely high uptake. The spleen and liver, which usually have the greatest activity, had a very low uptake in this method of delivery. This, of course, was primarily due to the size of the colloidal particles, which prevented absorption from the peritoneum.

TABLE 6.—*Injections into Peritoneal Cavity of Approximately 5 Mc. of Colloidal Gold*[198] *

Dog No.	26	27	28	15
Code No.	020045	020046	020047	020034
	Peritoneal Cavity			Intravenous (Saphenous Vein)
Right kidney	1.0	1.0	1.0	1.0
Left kidney	0.7	1.0	0.5	4.9
Liver—Serosal	0.5	0.9	0.1	287.0
Midserosal	8.1	1.1	0.3	...
Spleen—Serosal	3.0	1.1	0	20.2
Midserosal	1.5	0.7	2.0	...
Pancreas	0.7	6.7	283.2	0.2
Bladder	8.7	4.6	0.81	0.1
Lung	0.2	0.5	0.5	1.7
Heart	I †	0.1	0.1	1.7
Rib	0.6	0.9	3.9	4.3
Stomach	0.7	4.1	0.6	...
Small intestine	0.6	11.4	0.4	...
Large intestine	0.3	0.6	0.3	...
Peritoneum	12.1	10.2	6.7	0.6
Diaphragm	...	27.2	4.2	0.2
Omentum	419.6	313.5	...	...
Mesenteric node	...	1.5	0.98	2.2

* See footnote to Table 1.
† Infinitesimal.

URINARY BLADDER

In one dog the urinary bladder was filled with 5 mc. of radioactive gold which was allowed to remain for four hours. At autopsy activity in the bladder wall was found to be many times that in the intravenous control, as shown in Table 7.

FETUS

One dog was found to be pregnant at autopsy, and an assay of the fetus, which was practically at term, was made. The amniotic fluid, spleen, pancreas, liver and right kidney were assayed, as shown in Table 8. The activity found in all was infinitesimal, showing that the colloid did not pass through the placenta.

LIVER

Efforts at preventing localization of activity in the liver were undertaken. Table 9 shows studies of serial liver biopsies at intervals of several minutes. In Dog 23, after intravenous injection of 5 mc., activity from the liver showed a steady increase. At autopsy there was normal activity and normal distribution to other organs. In Dog 25 the portal vein and the hepatic artery were occluded for five minutes after intravenous injection. This prevented uptake of activity in the liver until the point at which the occlusion was released, at which time activity was immediately noticeable and at the end of 20 min. was almost the same as that in the dog in which no occlusion had occurred. The pick-up in the liver at autopsy

TABLE 7.—*Instillation into Urinary Bladder of Approximately 5 Mc. of Colloidal Gold*[198] *

Dog No.	29	19
Code No.	020048	020068
	Urinary Bladder, 4 Hr.	Intravenous (Jugular Vein)
Right kidney	1.0	1.0
Left kidney	1.1	0.5
Liver	1.4	196.0
Spleen	1.1	19.9
Pancreas	1.1	0.5
Bladder	87.6	0.1
Heart	0.6	0
Lungs	1.3	0.4

* See footnote to Table 1.

TABLE 8.—*Injection in Fetus of Dog 3* *

Code No.	020022	020068
Dog No.	30	19
	Fetus of Dog 3	Intravenous (Jugular Vein)
Right kidney	0.05	1.0
Liver	0.07	196.0
Pancreas	0.00	0.5
Spleen	0.04	19.9
Amniotic fluid	0.07	...

* Showing values of activity in organs, per gram weights, corrected for decay and in ratio to right kidney of parent (Dog 3). Autopsy was performed 2.7 days after injection.

was even higher than usual. After subcutaneous injection in Dog 24 the pick-up in the liver was very small in all biopsies and at autopsy. It was thought that if colloid could be prevented from going into the liver immediately after intravenous injection fixation might occur in other organs during the time of occlusion and the resultant distribution be altered. These experiments did not bear this out. However, it has been considered that by using occlusion of liver circulation with simultaneous arterial injection into another organ there might possibly be higher pick-up in that organ.

DISTRIBUTION IN HUMAN BEINGS

The autopsy findings in a 7-yr.-old boy with malignant hepatoma are presented in comparison to those in the dog. Administration of gold was intravenous, approximately 60 mc. being given over a period of two weeks. It is interesting to see that the tumor in the liver had little pick-up (Table 10).

TABLE 9.—*Multiple Liver Biopsies After Injection of Approximately 5 Mc. of Colloidal Gold*[198]*

Dog No.		23	25	24	15
Code No.		020042	020044	020043	020034
		Multiple Liver Biopsies			
			Occlusion of Portal Vein and Hepatic Artery for 5 Min.		
		Intravenous Injection No Occlusion	Intravenous	Subcutaneous	Intravenous Injection
Right kidney		1.0	1.0	1.0	1.0
Left kidney		0.3	1.4	3.4	4.9
Liver	0	10.15	0.92	0.37	...
	1	.....	0.64	0.50	...
	2	.....	0.30	0.22	...
	3	22.43	7.02	....	...
	4	.....	....	0.21	...
	5	34.01	6.72	....	...
Time in Minutes After Injection	6	.....	0.44	0	Release occlusion
	7	45.15	....	0.18	
	8	.....	8.77	....	...
	9	.....	....	1.38	...
	10	27.13	....	0.32	...
	15	28.78	47.56	....	...
	20	32.35	39.96	....	...
	25	27.27	....	....	...
At autopsy		150.2	398.4	9.2	287.0
Spleen		14.1	34.2	1.2	20.2
Pancreas		0.3	3.2	0.4	0.2
Bladder		I †	0.3	0.1	0.1
Lungs		0.6	I	0.3	1.9
Heart		0.1	16.2	0.1	1.7
Mesenteric node		0.2	....	0.6	2.2
Rib		6.4	7.9	0.3	4.3
Pleura—Parietal		1.7	0.2	0.3	...
Visceral		2.3	11.3	....	...
Stomach		0.1	0.3	0.1	...
Small intestine		0.1	0.4	0.2	...
Large intestine		0.1	0.5	0.1	...
Peritoneum		.....	0.3	1	...

* See footnote to Table 1.
† Infinitesimal.

TABLE 10.—*Differential of Gold Absorption Rate of Kidney (DAR[K]) in a 7-Yr.-Old-Boy with Malignant Hepatoma Who Had Received 60 Mc. Gold*[198] *Intravenously and in Dog 15, Which Had Received 15 Mc.*

	Intravenous Injection	
	Human Being DAR (K)	Dog 15 DAR (K)
Spleen	183.6	20.2
Liver	73.4	287.0
Liver tumor	0.5	....
Marrow—Vertebra	65.8	....
Marrow—Sternum	42.6	....
Rib	20.3	4.3
Adrenal gland	6.3	....
Lung	1.3	1.7
Kidney	1.0	1.0
Pleura	0.8	....
Peritoneum	0.5	0.6
Diaphragm	0.2	0.2
Heart	0.3	1.3
Pancreas	0.2	0.2
Bladder	0.1	0.1

CLINICAL APPLICATIONS

The clinical applications of arterial injection of radioactive isotopes are speculative at this time. However, because of evidence that localization can be obtained, it is reasonable to predict that occasions may arise on which this type of administration may be of value. Although gold has a short half-life and the impracticability of repeated arterial injections is recognized, longer-acting colloidal isotopes may overcome this failing. The fact that activity can be localized in the kidney or pancreas leads to the conclusion that almost any organ that has a specific blood supply can be injected with radioactive substances. The technique for each organ and the type of tumor sensitive to the various isotopes will have to be worked out with greater accuracy. Injection into the pleural space suggests the direct application of radioactivity into serous cavities that have been invaded by metastatic carcinoma. It is thought that by delivering radioactivity directly into serous cavities a certain amount of palliation may be obtained. Injection into the peritoneal cavity suggests the use of this type of administration in abdominal carcinomatosis, in which ascitic fluid and other discomforts may be relieved for variable periods. Localization in the urinary bladder wall suggests the possible use of this method for radiation of papillomatous tumors of the bladder. Many epithelial tumors of the bladder originate as seemingly benign papillomas which later prove to be malignant and which implant themselves on other portions of the bladder wall. A radioactive colloidal solution introduced into the bladder would completely surround the papilloma, so that excellent cross-fire radiation of the entire papilloma could be delivered. The uniform radiation of the bladder wall might well sterilize other small tumors not visible with the cystoscope. Intravenous injections may possibly be used for radiation of tumors in the liver or spleen, and the high pick-up found in the medullary spaces of the ribs and vertebrae suggests the possibility of using this method for some of the blood dyscrasis.

SUMMARY

Radioactive colloidal gold[198] was administered to dogs by intravenous, intra-arterial, intraperitoneal, intrapleural, and intravesicular routes. A certain amount of localization was achieved in various organs. While this work was carried out on a limited number of dogs and should be repeated many times, it is thought that the localization obtained was sufficient to present this preliminary report and to point the way to future clinical localization of radioactive isotopes by direct surgical approach.

RADIOACTIVE ISOTOPES IN LOCALIZATION OF INTRACRANIAL LESIONS

A Survey of Various Types of Isotopes and "Tagged Compounds" Useful in the Diagnosis and Localization of Intracranial Lesions with Special Reference to the Use of Radioactive Iodine-Tagged Human Serum Albumin

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MINNEAPOLIS

DURING the last three years, a new method for diagnosis and localization of intracranial lesions has been developed.[1] This method involves the use of radioactive isotopes or compounds tagged with a radioactive isotope, which when given to the patient are taken up preferentially by intracranial lesions. When the calvarium is monitored with a Geiger-Müller counter, a focus of high uptake designating a certain pathological process involving that part of the brain can be obtained. Thus, it is possible to locate the lesion in a majority of patients.

For many years, it has been known that the central nervous system possesses a peculiar defense mechanism, the so-called blood-brain barrier (B. B. B.), which protects the system by preventing toxic substances from getting into the nervous tissue. For example, in jaundiced patients, tissues other than that of the central nervous system may be highly tinged with bile pigments; the nervous tissue alone remains colorless. It is only in those instances in which the presence of bile salts and pigments in the blood stream over a long time has finally injured and thus disrupted the blood-brain barrier that the central nervous system may show some discoloration. This fact alone demonstrates the presence of such a barrier. Likewise, when a part of the central nervous system is diseased, be the disease neoplastic or inflammatory, the blood-brain barrier is likely to be broken. Therefore, substances which are normally kept from entering the central nervous system may go through the disrupted barrier into the nervous tissue. This is the fundamental

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1. Moore, G. E.; Kohl, D. A.; Wang, J. C., and Caudill, C. M.: Biophysical Studies of Methods Utilizing Fluorescein and Its Derivatives to Diagnose Brain Tumors, Radiology **55**:344-356, 1950. Moore, G. E.; Peyton, W. T.; French, L. A., and Walker, W. W.: The Clinical Use of Fluorescein in Neurosurgery: The Localization of Brain Tumors, J. Neurosurg. **5**:392-398, 1948.

principle on which diagnostic procedures for intracranial lesions using radioactive isotopes or tagged compounds are based. However, there are undoubtedly many other contributing factors, such as changes in the serum protein under certain pathologic conditions, that might come into play. These additional factors will not be discussed in this report. It is the purpose of this paper to review the various isotopes and "tagged" compounds available for the diagnosis of intracranial lesions, with their merits and disadvantages, and to reexamine past experience in order to plan better for the future.

I. RADIOACTIVE PHOSPHORUS (P^{32})

It has been shown by Selverstone [2] that P^{32} would concentrate in cerebral tumors in significantly greater amount than in normal gray and white matter. The radioactivity of tumor tissue ranged from 5.8 to 110 times greater than that of adjacent white matter.[3] Normal gray matter, perhaps because it has more cellularity, has more radioactivity than white matter, usually one to two times more.[3] P^{32} has a half-life of 14.3 days and a maximum energy of beta radiation of 1.69 mev. It has been shown that this amount of energy can penetrate approximately 7 mm. of brain tissue.[4] Therefore, it is of no value for preoperative localization since the beta rays cannot be directly detected outside the calvarium. However, Selverstone and his associates have used P^{32} for localization of intracranial tumors at the time of operation. A special Geiger-Müller counter similar in form to an ordinary brain needle was built to be inserted into the cerebral tissue for probing purposes. This counter is connected to a preamplifier and a scaler which are brought into the operating room. In a series of 33 tumors, of which 23 were subcortical, 29 were localized by this method.[5]

The method under discussion may be of some value in neurosurgery; however, it is still far from being ideal. In the first place, it is feasible only when a bone flap has been reflected or the skull perforated. Therefore, it cannot aid in the preoperative decision of whether or not a craniotomy should be performed. In the second place, the level of radioactivity of a control area must be determined by inserting the counter into "normal" brain tissue at various depths for comparison with the counting rates of the suspected area. This procedure involves a certain amount of time-consuming probing and is not entirely innocuous. One of its best uses, as outlined by Selverstone, is the more accurate determination of the gross infiltration of malignant gliomas so that more adequate radical resection can be performed.

II. RADIOACTIVE POTASSIUM (K^{42})

It is obvious that the greater the differential uptake between the tumor and normal brain tissue, the more efficient and accurate the localization will be. K^{42} has strong beta as well as gamma emission (beta—75%, 3.58; 25%, 2.07 mev;

2. Selverstone, B., and Solomon, A. K.: Radioactive Isotopes in the Study of Intracranial Tumors: Preliminary Report, Tr. Am. Neurol. A., pp. 115-119, 1948.

3. Selverstone, B.; Solomon, A. K., and Sweet, W. H.: Localization of Brain Tumors by Means of Radioactive Phosphorus, J. A. M. A. **140**:277-278 (May 21) 1949.

4. Glendenin, L. E.: Determination of Energy of Beta Particles and Photons by Absorption, Nucleonics **2**:12-32, 1948.

5. Selverstone, B.; Sweet, W. H., and Robinson, C. V.: The Clinical Use of Radioactive Phosphorus in the Surgery of Brain Tumors, Ann. Surg. **130**:643-651, 1949.

gamma—1.51 mev), and for reasons not yet clear the uptake of K^{42} by tumor tissue in contrast to that by normal tissue is very high. Selverstone [6] has reported a differential uptake by a glioma of over 200 times the level of normal brain. It seems, therefore, that K^{42} should be an ideal isotope for localization of tumors. However, practical experience has almost excluded it as the agent of choice because of the following apparent reasons: A. Its half-life, 14.2 hr., although desirable for physiological safety purposes, is too short to be of practical value. It cannot be stored for clinical use as can P^{32} or I^{131}. Clinics at a distance from the source of supply will find it extremely expensive to use. B. Another result of the rapid decay rate is the necessity of using relatively large amounts of potassium in order to obtain sufficiently high levels of radioactivity. C. The energetic gamma emission increases radiation hazards and therefore necessitates heavy, bulky shielding. D. The high concentration of K^{42} in muscle makes it difficult to detect tumors near the base of the skull. This is especially true of tumors in posterior fossa, where a thick layer of muscles intervenes between the brain tissue and the counter.

III. RADIOACTIVE IODINE (I^{131})

Radioactive iodine has up to this time proved to be most adaptable for tagging various compounds and therefore has gained the widest acceptance. Whereas P^{32} and K^{42} are used by themselves, I^{131} has always been incorporated into chemical combination with other substances, of which diiodofluorescein is the best known. Recently radioactive iodine-tagged human serum albumin has been used, and it also appears to be a suitable compound. For purpose of discussion, the two compounds will be dealt with separately.

1. *Diiodofluorescein (DIF).*[7]—Fluorescein and diiodofluorescein must not be confused. Both are now used for neurosurgical diagnosis and localization. Fluorescein is an acid chromagen dye to which a pathologic blood-brain barrier is readily permeable but which stains only minimally normal brain tissue. Therefore, with its special property of being fluorescent in high dilution under ultraviolet illumination, differential staining of various tissues can be easily detected. In this clinic, fluorescein has been successfully used for localizing brain tumors during operation. Briefly, the technique is to aspirate with a brain needle from the suspected site in the brain of a patient who has been given 10 cc. of 10% fluorescein sodium one hour preoperatively. The aspirated tissue is then examined under ultraviolet light, and fluorescence establishes the presence and location of a lesion. More than 300 patients have been subjected to the fluorescein technique at this clinic during the last three years, with less than 1% error in the interpretation of the presence or absence of tumor in the biopsy material.

Diiodofluorescein, on the other hand, is a tagged compound. It has almost no fluorescence and is therefore of no value in localizing tumors during operation. However, when synthesized with radioactive iodine (mev, gamma 0.367, beta 0.6) it can be used as a tracer agent preoperatively. The technique of the test has been described elsewhere.[1] Using this agent, Davis and Ashkenazy were able to estab-

6. Selverstone, B.: Radioactive Potassium, A New Isotope for Brain Tumor Localization, read before the Clinical Congress of the American College of Surgeons, 1950.

7. Obtained from the Abbott Laboratories, North Chicago, Ill.

lish accurate diagnosis and localization in 95% of 340 patients tested.[8] There are several important advantages to the use of diiodofluorescein that deserve emphasis here. It is secreted rapidly by the liver. It is not metabolized in man, and therefore relatively large amounts can be given without danger of injury to the thyroid gland by I^{131} split off the molecule. Quick disappearance of the dye from the blood stream increases greatly the accuracy of localization because this allows the increased radioactivity retained in the brain tumor to stand out in relief when surrounding blood and tissue radioactive content is low. There have been no side effects, systemic or local, as a result of diiodofluorescein administration. Therefore, until a better radioactive medium is developed diiodofluorescein remains the agent of choice.

2. *Radioactive Iodinated Human Serum Albumin (RIHSA).*[7]— Radioactive iodinated human serum albumin has been used by various groups to determine the

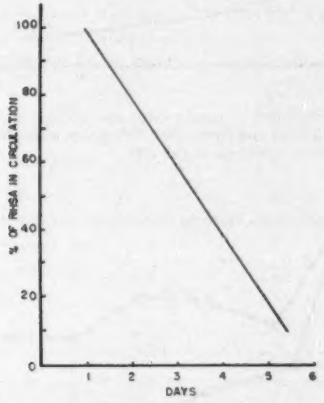

Fig. 1.—Curve showing disappearance of RIHSA in blood.

plasma volume in human beings.[9] A patient suspected of having a brain tumor was given an injection of RIHSA as a part of a study to determine the usefulness of the technique for determining blood volumes. The patient's head was monitored and an increased level of radioactivity recorded over the presumed site of the lesion. Eventually the localization indicated by this difference in radioactivity was confirmed by other diagnostic procedures, and it was finally proved at operation. Since then eight patients have been studied with the use of this compound. We were able to localize the tumors in four cases and to rule out tumor in two in which subsequent air studies and angiograms gave negative results. The remaining two patients were still undergoing study.

8. Davis, L.; Martin, D.; Ashkenazy, M.; LeRoy, G. V., and Fields, T.: Radioactive Diiodofluorescein in Diagnosis and Localization of Central Nervous System Tumors, J. A. M. A. **144**:1424-1432, 1950.

9. (*a*) Fine, J., and Seligman, A. M.: Traumatic Shock, (Dec. 23) J. Clin. Invest. **22**:285, 1943. (*b*) Storaasli, J. P.; Krieger, H.; Friedell, H. L., and Holden, W. D.: The Use of Iodinated Plasma Protein in the Study of Blood Volumes, Surg., Gynec. & Obst. **91**:458, 1950.

Metabolic studies in both animals and human beings have shown that RIHSA, when given intravenously, remains in the blood stream a long time (Fig. 1). A great part of it is apparently metabolized by the body and iodine liberated. Although most of the free iodine is excreted through the urine, approximately 5% of it is

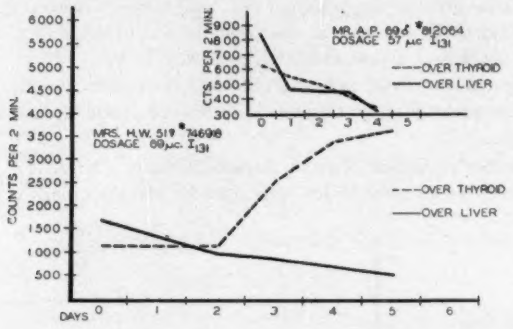

Fig. 2.—Comparison of thyroid I^{131} uptake with and without stable iodine preparation of the patient. Daily counts over thyroid and liver, after I^{131} given intravenously. Mr. A. P. was given strong iodine solution for 48 hr. previous to the test.

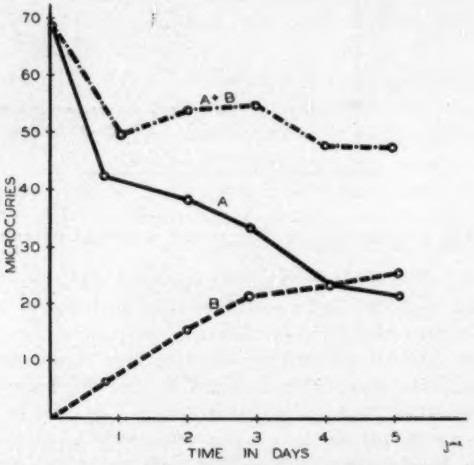

Fig. 3.—Urinary excretion of RIHSA. *A*, blood level of RIHSA remaining in vascular tree on days subsequent to intravenous administration. *B*, amount of RIHSA excreted in the urine daily sample being added to the total. $A + B$, sum of RIHSA left in blood stream and excreted in the urine.

taken up by the thyroid gland by the end of 24 hr.[9b] This, of course, raises the question of whether or not the thyroid gland may be injured by the radioactive iodine. It is, however, possible to prevent this deposition of iodine in the thyroid. It has been shown that administration of stable iodine as strong iodine solution

U. S. P. (Lugol's solution) starting 24 hr. previous to the test will block the uptake of the radioactive iodine by the thyroid and thereby eliminate the danger of overradiation (Fig. 2). A small amount of RIHSA is not metabolized; it diffuses out into the tissue and the lymphatic vessels unchanged. One hour after administration about 1 to 2% of the tagged albumin can be recovered from the thoracic duct.[9b] The liver apparently does not participate in the metabolism or excretion of RIHSA. In experimental animals, it has been shown that there is only a negligible amount of this substance in the bile.[9b] The excretion of I^{131} after RIHSA administration is mainly by way of the kidneys. At the end of the first day, the total urinary excretion reaches about 15 to 20% of the total amount given (Fig. 3). It is evident, therefore, that it would take about a week to excrete RIHSA completely. As the blood level gradually decreases, the tissue level also falls. Eventually, all of it is excreted by the kidneys.

Counts in a Patient Given 450 μc. of RIHSA Intravenously

	Area	Counts per Minute	Difference, %
	First Survey, One Hour After Administration		
L_2 / R_2	Lateral frontal	948 / 991	L, 1.5%
L_3 / R_3	Ear line (temporal-parietal)	625 / 688	R,* 9%
L_4 / R_4	Mastoid region	801 / 793	L, 1%
	Second Survey, 30 Hours After Administration		
L_2 / R_2	Lateral frontal	581 / 617	R, 6%
L_3 / R_3	Ear line (temporal-parietal)	486 / 563	R, 14%*
L_4 / R_4	Mastoid region	535 / 537	0

* Site of tumor; craniotomy revealed a deep temporoparietal ependymoblastoma invading the internal capsule and thalamus.

Note that on the first day there was only 9% difference between the tumor side and the opposite side. On the second day the difference increased to 14%.

It is important, for the purpose of obtaining counts during the optimal time when ratio between tissue concentration and blood concentration is the greatest, that daily counts be made for two to three days. A focus of higher activity demonstrated on the first day after injection should persist through the second and third days. In fact, the difference in uptake between the site of the lesion and the symmetrical contralateral normal area should increase on the second and third day. The case recorded in the Table will illustrate this point.

RIHSA does have some disadvantages. First, a relatively large dose has to be given (400 to 500 μc have been given at this clinic in limited trials) in order to obtain a significantly high counting rate. Thus, the danger of excessive I^{131} uptake cannot be ignored even though the patient has been adequately prepared with the use of strong iodine solution and the thyroid gland is not subjected to more radiation than the amount present in the circulating blood. Experience with this compound is still too limited to be certain that there is no danger of excessive thyroid radiation. In addition, special precautions must be taken by the hospital staff to avoid contamination, since excretion of RIHSA is mainly through the urine.

SUMMARY

If further study reveals that diiodofluorescein sodium is actually bound to the serum proteins, its use is, in reality, just another way of tagging the protein. The use of RIHSA accomplishes the same thing more directly but has the added risk of releasing free radioactive iodine.

Obviously, the techniques discussed are probably not the best ways of utilizing the blood-brain barrier phenomenon for clinical uses. In the near future other isotopes or isotope-tagged compounds which can be more efficiently employed will probably be discovered.

In addition, improvement in instrumentation are continuing. At this clinic scintillation type counters have increased the counting rates obtained threefold. Multiple counters will obviate much of the labor and inconvenience resulting from prolonged surveys necessitated by present equipment.

USE OF INVERT SUGAR SOLUTIONS FOR PARENTERAL FEEDING OF SURGICAL PATIENTS

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FOR MANY years dextrose has been the principle agent used for supplying carbohydrates parenterally to the surgical patient. Basic caloric requirements can be met, protein catabolism reduced and some protection of the liver afforded if dextrose is given in sufficient quantity. However, prolonged infusions of huge volumes of fluid are required if the usual 5% solution is employed. The 10% solution has the disadvantage of causing diuresis and glycosuria, with resulting loss of essential water and calories. The combination of alcohol with dextrose, while effective, results in prolongation of the infusion time far beyond practical limits. Fat as a source of calories for parenteral administration is still in the experimental stage, though it may be in the future the answer to this problem.

In the search for a more suitable agent for parenteral nutrition invert sugar has been suggested. It was decided to compare its utilization with that of dextrose. Invert sugar is hydrolyzed sucrose and therefore consists of a mixture of equal parts of glucose and fructose. It has been shown in both animals [1] and human beings [2] that the tissues utilize fructose more readily because of its more rapid phosphorylation. Invert sugar, because of its fructose content, might offer an inexpensive but effective substitute for dextrose alone.

METHODS OF INVESTIGATION

Subjects in this study were both preoperative and postoperative patients. The ages varied from 42 to 78 yr. Prior to the study, all patients had normal urine, blood sugar, and nonprotein nitrogen. Each received an infusion of either dextrose or invert sugar on the first day, and on the following day the other sugar was given at the same rate and under the same conditions. Blood sugar levels were determined prior to and at the midpoint of infusion, at the termination of infusion and two hours afterward. Urine specimens were collected at the completion of fluid administration and again 3 and 24 hr. later. The Folin-Wu analysis for reducing sugar was carried out on the refrigerated collected specimens for each day. No attempt was made in the present study to determine the blood or urine fructose levels.

From the Department of Surgery, University of Wisconsin Medical School.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 24, 1951.

1. Cori, C. F.; J. Biol. Chem. **70**:577-585, 1926.

2. Weichselbaum, T. E.; Elman, R., and Lund, R. H. Proc. Soc. Exper. Biol. & Med. **75**:816-818, 1950.

TABLE 1.—*Group I. Normal Subjects Receiving 1,000 Cc. of Ten per Cent Invert Sugar or Dextrose at the Rate of 1.5 Gm. per Kilogram per Hour*

Patient	Maximum Blood Sugar Level, Mg. per 100 Ml.		Urinary Sugar Excretion, Gm.	
	Dextrose	Invert Sugar	Dextrose	Invert Sugar
1	444	405	13.6	10.6
2	483	482	26.7	26.0
3	468	456	3.8	10.0
4	280	272	0.0	4.5
5	507	444	22.8	37.0
6	408	304	33.0	4.5
7	546	498	26.0	6.0
8	498	364	33.0	20.0
9	483	364	11.0	0
10	456	364	12.0	20.0
Averages	457.3	396.7	18.7	13.8

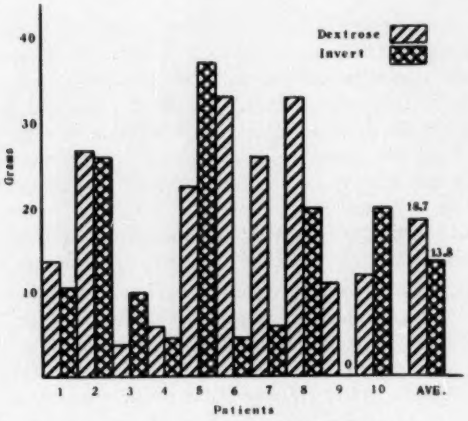

Fig. 1.—Urinary sugar excretion in Group I.

RESULTS

Group I was comprised of 10 normal subjects awaiting surgical intervention (Table 1). Each received 1000 cc. of 10% dextrose or invert sugar intravenously at a rate of 1.5 gm. per kilogram per hour. On the following day the other solution was given. Glycosuria resulted in all but one instance. However, the average urinary sugar excretion with dextrose was 18.7 gm., while the average "spill" with invert sugar was 13.8 (Fig. 1). Blood sugar levels were consistently higher when dextrose was given, the average maximum being 457 mg. per 100 cc., as compared to 396 mg. with invert sugar (Fig. 2). Average urinary output for the period during and three hours after infusion was 845 cc. with dextrose and 744 cc. with invert sugar.

Group II consisted of seven postoperative patients who had been in marked negative caloric and nitrogen balance for a long time. Each was given 1,000 cc. of 10% dextrose or invert sugar on succeeding days in approximately one hour,

with no attention paid to the amount per kilogram per hour (Table 2). The average amount of reducing substance in the urine with dextrose was 29 gm., while only 9 gm. was lost when invert sugar was used (Fig. 3). Again dextrose resulted in slightly higher blood sugar levels (Fig. 4).

The third and largest group was composed of 15 routine postoperative cases; the patients received 2,000 cc. daily of either 10% dextrose or invert sugar in approximately two hours (Table 3). Every patient excreted more reducing substance in the urine when dextrose was used. The average urinary sugar excretion with dextrose was 56.2 gm., while the excretion with invert sugar averaged 31.5 gm. (Fig. 5). The average urine volume when dextrose was administered was 1,566 cc.

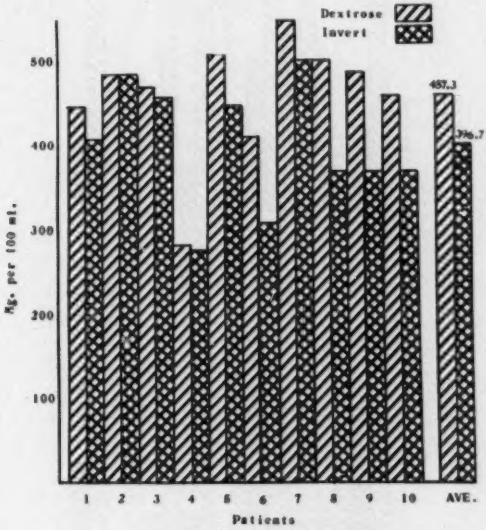

Fig. 2.—Maximum blood sugar level in Group I.

TABLE 2.—*Group II. Postoperative Patients Receiving 1,000 Cc. of Ten per Cent Dextrose or Invert Sugar in One Hour*

Patient	Maximum Blood Sugar Level, Mg. per 100 Ml.		Urinary Sugar Excretion, Gm.	
	Dextrose	Invert Sugar	Dextrose	Invert Sugar
1	400	456	31.2	9.6
2	390	332	6.7	5.3
3	416	378	36.3	21.5
4	390	480	57.9	18.9
5	456	296	8.6	2.2
6	528	332	24.0	5.4
7	342	228	38.9	0
Averages	417	374	29.0	8.9

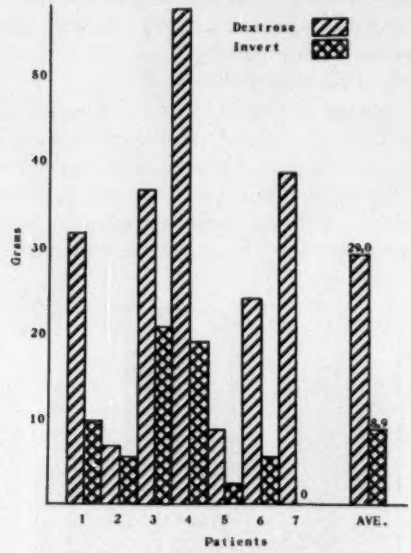

Fig. 3.—Urinary sugar excretion in Group II.

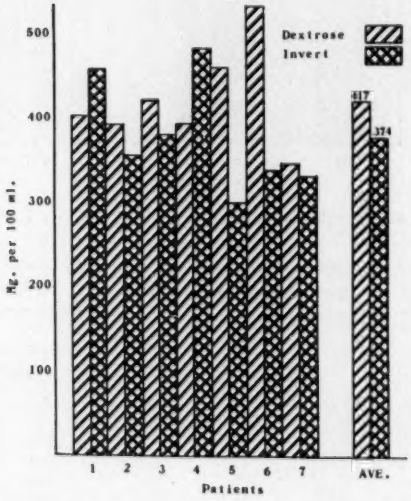

Fig. 4.—Maximum blood sugar level in Group II.

TABLE 3.—*Group III. Postoperative Patients Receiving 2,000 Cc. of Ten per Cent Dextrose or Invert Sugar in Two Hours*

Patient	Maximum Blood Sugar Level, Mg. per 100 Ml.		Urinary Sugar Excretion, Gm.	
	Dextrose	Invert Sugar	Dextrose	Invert Sugar
1	498	456	124.0	30.2
2	483	378	31.3	26.0
3	416	483	67.0	43.4
4	513	304	36.8	0
5	498	498	49.0	15.2
6	528	420	43.0	38.2
7	513	424	39.4	27.3
8	500	492	63.8	49.0
9	615	522	56.8	36.1
10	528	483	59.9	51.6
11	498	452	53.5	42.0
12	528	468	80.1	13.4
13	606	507	31.5	22.2
14	528	555	68.4	43.6
15	410	280	37.8	34.2
Averages	510	444.8	56.2	31.5

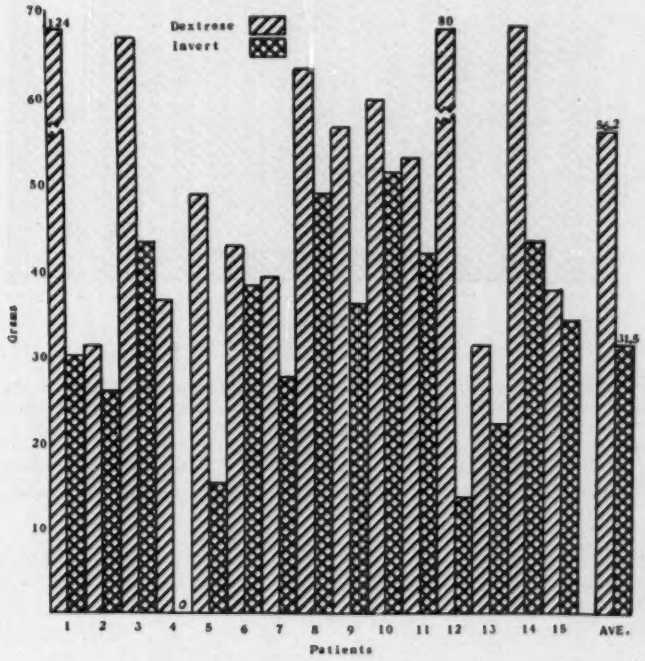

Fig. 5.—Urinary sugar excretion in Group III.

and when invert sugar was given, only 1,054 cc. Blood sugar levels were significantly higher with dextrose (Fig. 6).

The fourth group of eight patients consisted of four who received 1,000 cc. of 5% dextrose or invert sugar in one hour and four who received 2,000 cc. of the same solution over a two-hour period. The four receiving 1,000 cc. of either solution showed no reducing substance in the urine. On the other hand, when 2,000 cc. was given, an average loss of 14 gm. was noted with dextrose while there was an average loss of 9 gm. with invert sugar. Blood sugar levels with dextrose were, as in the previous studies, somewhat higher (Table 4).

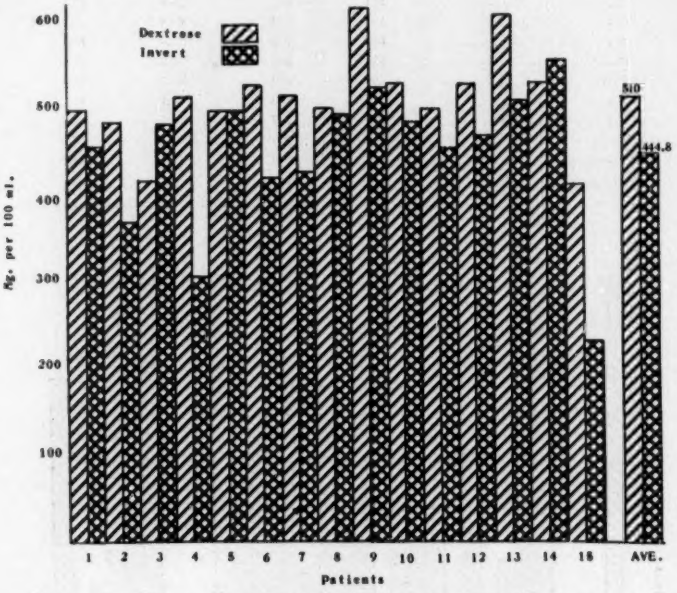

Fig. 6.—Maximum blood sugar level in Group III.

TABLE 4.—*Group IV. Patients Receiving Five per Cent Dextrose or Invert Sugar in One Hour*

Patient	Maximum Blood Sugar Level, Mg. per 100 Ml.		Urinary Sugar Excretion, Gm.	
	Dextrose	Invert Sugar	Dextrose	Invert Sugar
Patients Receiving 1,000 Cc.				
1	312	272	0	0
2	230	180	0	0
3	250	238	0	0
4	352	280	0	0
Averages	286	242.5	0	0
Patients Receiving 2,000 Cc.				
1	410	352	6.0	0
2	272	210	10.0	20.0
3	364	420	31.0	17.0
4	410	296	10.0	0
Averages	364	319.5	14.0	9.2

COMMENT

Weinstein [3] has recently enthusiastically reported 98.4% utilization of invert sugar. Our studies under similar conditions show a utilization of 86%, only a 5% improvement over dextrose when 1,000 cc. of 10% solution was employed. The greatest differences between dextrose and invert sugar were observed in emaciated patients or when 2,000 cc. of 10% solution was used. In the emaciated patients there was 91% utilization with invert sugar and only 71% with dextrose. When 2,000 cc. of 10% solution was provided in two hours in routine postoperative cases, the average retention was about 600 calories in patients receiving dextrose, while those receiving invert sugar retained approximately 700 calories. This additional 100 calories may be of significance in protecting protein stores of the surgical patient.

Except in our first group, no attempt was made to administer the fluids on the basis of milligrams per kilogram per hour. In the first place this method would be impractical in most hospitals. Secondly, the weight of the patient does not have a direct relationship to the ability of the cardiovascular system to handle fluids given intravenously. For example, an extremely obese patient on this regimen might receive 2,000 cc. of fluid in one hour. This large volume rapidly administered could well lead to cardiac embarrassment.

CONCLUSIONS

1. It would appear that invert sugar, while not ideal, is a definite improvement over dextrose.

2. With 5% solution, no significant advantage is observed in the parenteral use of invert sugar over dextrose.

3. A 10% solution of invert sugar can be given more rapidly and is more completely utilized than dextrose, and it will provide an additional 100 calories when 2,000 cc. are given.

4. In general, diuresis is less with intravenous administration of invert sugar than with dextrose.

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3. Weinstein, J. J.: Ann. West. Med. & Surg. 4:373-377, 1950.

TRYPTIC DÉBRIDEMENT OF NECROTIC TISSUE

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RICHARD PATTON, M.D.
AND
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THE USE of pure, crystalline trypsin in the enzymatic débridement of fibrinopurulent empyema was reported in October, 1950, by Reiser, Roettig and Curtis.[1] From this investigation it became evident that its use in treating other necrotic and purulent lesions might offer a marked improvement in or addition to present therapeutic measures. Accordingly, the scope of the investigation was enlarged to try the efficacy of trypsin in a variety of suppurative and sloughing lesions. This is a preliminary report of the results obtained.

The enzymatic digestion of necrotic tissue has a historical background of many years, but its practical application has been given little attention. John Hunter was the first surgeon to demonstrate the digestion of dead tissue by animal proteolytic enzymes. Since Hunter's time numerous proteolytic enzymes of both plant and animal origin have been discovered. However, there has been little or no work done to apply these in the problem of treating suppurative or necrotizing lesions in man. It is interesting to note that Miller [2] discovered that trypsin was the enzyme system most uniformly found in the excreta of maggots.

In 1948, being disappointed in the results of the local instillation of streptomycin in tuberculous empyema, we decided to try crystalline trypsin for enzymatic débridement of the pyogenic membrane of the empyema cavity. About the same time Dr. W. S. Tillett and his co-workers [3] began to investigate the use of enzymatic débridement in nonspecific empyema. These investigators had for a number of years been experimenting with the enzymes streptokinase and streptodornase, proteolytic

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Resident in Research Surgery (Dr. Reiser); Assistant Professor of Clinical Surgery (Dr. Patton); Assistant Professor of Research Surgery (Dr. Roettig).

From the Department of Research Surgery and the Department of Surgery of the Ohio State University and the Surgical Service of White Cross Hospital.

1. Reiser, H. G.; Roettig, L. C., and Curtis, G. M.: Tryptic Débridement of Fibrino-Purulent Empyema, in Proceedings of the Forum on Fundamental Surgical Problems, Surgical Forum of the American College of Surgeons, 1950, Philadelphia, W. B. Saunders Company, 1951, pp. 17-24.

2. Cited by Fletcher, F., and Haub, J. G.: Digestion in Blowfly Larvae, Phormia Regina Meigen, Used in the Treatment of Osteomyelitis, Ohio J. Sc. **33**:101 (March) 1933.

3. Tillett, W. S.; Sheery, S.; Christensen, L. R.; Johnson, A. J., and Hazelhurst, G.: Streptococcic Enzymatic Débridement, Ann. Surg. **131**: 12-22 (Jan.) 1950.

enzymes of streptococcal origin. Meanwhile in Germany Kurt Stucke [4] reported in 1949 on the successful use of a trypsin preparation in the enzymatic débridement of burns.

In vitro, trypsin quickly and quantitatively digests fibrin and clotted blood. Its action on other body tissues was determined in the following manner (Fig. 1). Sections of gangrenous skin, normal skin, fat, fascia, blood vessels and muscle were cut, each weighing 1 gm. One section of each tissue was placed in a flask containing 250 mg. of trypsin dissolved in 25 cc. of Sorensen's phosphate buffer at a pH of 7.1. A second gram of each tissue was placed in a flask containing the diluent only. Both series of flasks were then incubated at 37 C. for 72 hr. The effect and degree of digestion were then compared. Maximum digestion occurred within 24 hr. Muscle tissue showed the greatest degree of digestion. It was reduced to a gelatinous friable mass. The other tissues showed partial digestion, as evidenced by the gray, swollen and feathery appearance of the sections (Fig. 2*A*). A second series of flasks was then incubated containing twice as much trypsin. These showed an almost quantitatively greater amount of digestion.

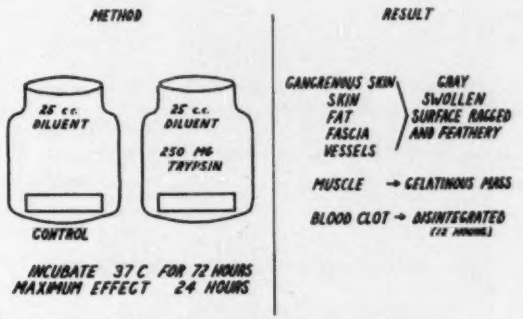

Fig. 1.—Diagrammatic representation of the method of testing the proteolytic activity of trypsin in vitro.

When applied to a purulent and necrotic lesion, trypsin rapidly lyses the fibrinous strands and coagulum on the surface of the lesion. This lysis takes place in a matter of minutes. It digests the slimy and viscid coating of desoxyribose nucleoprotein of the purulent exudate and then attacks any dead tissue in the lesion. There is an almost immediate outpouring of serum, which floats off the digested debris. The exudate becomes thin and serous. With this, fresh, viable leucocytes appear. Bacteria rapidly decrease in number and finally may disappear completely. As treatment is continued the exudate decreases or ceases. A clean granulating, pink surface is left.

The decrease or disappearance of infecting organisms from the lesion is remarkable. As previously reported, even tubercle bacilli disappear from an empyema cavity. This phase of the investigation is being carried on by Dr. J. M. Birkeland, of the Department of Bacteriology at Ohio State University, and will be reported separately. Trypsin does not kill or directly digest tubercle bacilli. Its effect on other organisms is still being determined. The disappearance of bacteria from the

4. Stucke, K.: Digestion of Slough by Pancreatic Ferment in Treating Severe Burns, Chirurg. **20**: 588-595 (Nov.) 1949.

lesion seems to be due to a strengthening of the humeral elements of defense and a clearing of debris. By clearing the wound of slough and debris, trypsin denies a medium to the bacteria. The outpouring of fresh leucocytes increases the phagocytosis of bacteria.

Certain general rules have been found concerning the use of trypsin which must be followed to obtain successful results (Table). Tryptic acivity is optimal within the pH range of 6.8 to 7.5. Therefore, when used in cavities trypsin should be employed in a solution of Sorensen's phosphate buffer. On surface lesions the pH of the surface should be tested, and if it is extremely alkaline or moderately acid the trypsin in buffered solution should be used as a wet dressing. Most surface lesions, however, have been found to be within the optimal pH range. When this is true and when the exudate is slightly moist, the trypsin crystals may be powdered directly on the wound. When an eschar is present or the exudate is dry and encrusted, trypsin should always be used first in buffered solution as a wet dressing. Slight mechanical loosening of the edges of the eschar or crust before application hastens its removal.

A second factor to be considered in the surface application of trypsin is the effect of temperature. Lowering below body temperature rapidly inactivates trypsin. Therefore, external heat should be applied to the wet dressing.

Method of Application of Trypsin in Surface Lesions

Powder	Solution
1. Applied by dusting direct or with atomizer; must be moist area	1. 0.5% solution
2. Wound should be alkaline Test with nitrazine paper	2. Intermittent injection into wet dressing as in dakinization
	3. Mild external heat
	4. Preferred for use on dry crust or eschar
Not painful	
No effect on surrounding skin or on living tissue at base of wound	

Thirdly, the time element is of importance. When allowed to stand in solution at room temperature, trypsin loses 75% of its activity in three hours, and therefore continuous effectiveness should not be expected. To achieve constant tryptic activity, the dressings should be changed every three or four hours, or tubes should be incorporated in the dressing through which freshly prepared trypsin solution should be instilled at three-hour intervals.

When trypsin is employed in a body cavity where continuous absorption may occur, as in an empyema cavity, a histamine-like reaction may take place with the first two or three treatments.[5] As shown in our previous paper, this may be prevented by the prior administration of 25 to 50 mg. of diphenhydramine (benadryl®) hydrochloride intravenously followed by the oral administration of 50 to 100 mg. at three-hour intervals for three doses. Thereafter no benadryl® is needed. When trypsin is used on surface lesions no histamine-like reaction has been noted and no benadryl® protection is necessary. When it is used in cavities, the only side reaction noted has been a mild temperature elevation and increased pulse rate. When used on the surface, the only reaction complained of has been a mild sensation of burning or

5. Wells, J. A.; Morris, H. C., and Dragstedt, C. A.: Significance of Histamine in Trypsin Shock as Determined by Benadryl, Proc. Soc. Exper. Biol. & Med. **62:** 209-213 (June) 1946.

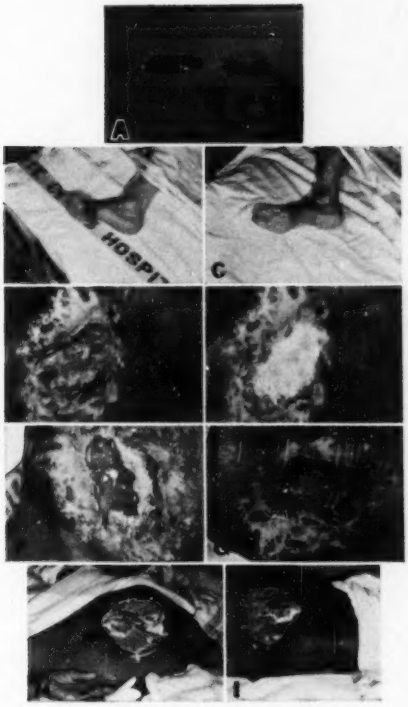

Fig. 2.—*A*, the effect of tryptic digestion of muscle tissue. Normal muscle, right; muscle subjected to tryptic digestion for 72 hours, left. *B*, gangrenous diabetic ulcer of the foot prior to trypsin therapy. *C*, the same lesion after tryptic débridement. *D*, necrotic lesion of right thigh following failure of skin graft. *E*, same lesion covered with crystalline trypsin. *F*, same lesion, illustrating the outpouring of clear, fresh serum following the application of powdered trypsin to the lesion. *G*, same lesion, showing the final result of tryptic débridement. *H*, decubitus ulcer of the sacral region showing a marked purulent exudate and exposed necrotic sacrum prior to tryptic débridement. *I*, same lesion after the use of crystalline trypsin showing the marked cleansing and improvement in the soft tissue. The exposed bone was unaffected.

stinging of the treated area. The activity of trypsin may be stopped immediately by irrigating the treated area with sodium bicarbonate solution.

We feel that trypsin is the ideal agent for enzymatic proteolytic débridement because it is available in pure crystalline form in vials of standardized potency and stabilized strength. It is supplied in sterile vials under the name of "tryptar" [6] by the Armour Laboratories.

The various conditions in which "tryptar" has been tried will be discussed, with illustrative case reports.

TUBERCULOUS EMPYEMA

Tuberculous empyema was the first lesion in which we used tryptic débridement. The following case from our empyema series is a good example.

H. M., a Negro, 28 yr. of age, first was told he had empyema two years prior to his admission to the hospital. Its etiology was not determined. Three months before his admis-

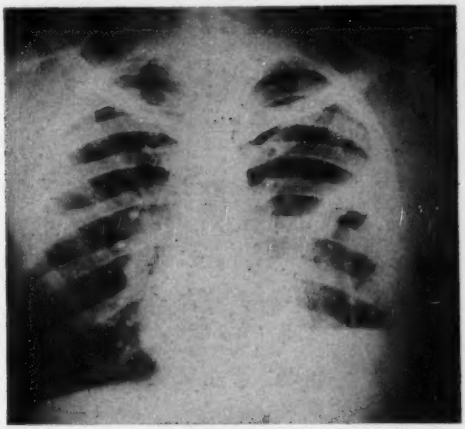

Fig. 3.—Roentgenogram of the chest of a patient with tuberculous empyema and calcification of the pleura prior to tryptic débridement and decortication.

sion a diagnosis of pulmonary tuberculosis with empyema was made (Fig. 3). The sputum was positive, as was the smear of the empyema fluid. Irrigation, aspiration and instillation of streptomycin were tried for one month, without improvement. The patient was then given 12 daily treatments of "tryptar." On the 12th day the smear of the empyema fluid showed no tubercle bacilli. The following day thoracotomy and decortication were performed. A thick, calcified pleura was found and removed. The surface of this was clean, and some of the calcium had been loosened from the surface. The patient made an uneventful recovery. Sedimentation rate dropped from 58 to 3 mm. per hour. The sputum is now negative (Fig. 4).

GROSSLY CONTAMINATED AMPUTATION STUMP

The following case showed an excellent response to "tryptar."

E. K., a 31-yr.-old white man, was admitted to the hospital in profound shock with a severely crushed and macerated right leg, grossly contaminated with street grime. A guillotine amputation was performed through the femoral condyles and bleeding stopped as a lifesaving measure.

6. Trademark registration applied for.

Some contaminated tissue of questionable viability was left on. The patient was given penicillin parenterally and the stump treated with powdered "tryptar" on three successive days. A clean granulating stump was obtained which was secondarily closed on the 10th day. Convalescence was uneventful. It is felt that the use of "tryptar" spared the patient a higher amputation and materially shortened his hospitalization.

SUBCUTANEOUS HEMATOMA

The digestion of clotted blood by trypsin is rapid and completely effective. A large hematoma may be quickly and safely digested by trypsin in one treatment.

C. B., a 59-yr. old white man, was admitted to the hospital for the surgical treatment of varicose veins. Bilateral high and low saphenous ligations, with vein stripping on the lower part of the left leg, were performed. While the patient was convalescing, he was treated with cortisone for gout. The wound on the left leg failed to heal, and a large subcutaneous hematoma developed, measuring 10 cm. in diameter. When sutures were removed, the wound edges separated and the upper border of the clot was exposed. Three days later, "tryptar" was powdered over the visible portion of the clot. In a few minutes this was liquefied. More "tryptar" was sprinkled into the wound. This procedure was repeated five times in the next half-hour. The clot was completely digested. The leg was then wrapped with elastic bandage, and complete healing followed.

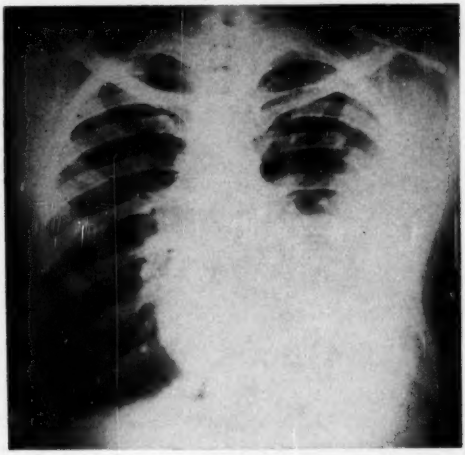

Fig. 4.—Postoperative roentgenogram of the chest of the patient in Figure 3, showing complete ablation of empyema space.

CHRONIC OSTEOMYELITIS

The possibility of clearing up chronic osteomyelitis with trypsin alone does not seem likely. As an addition to other therapy, however, there would seem to be a definite use for it. In the following case many other forms of therapy had been tried. Trypsin applied locally seemed to be the deciding factor in a satisfactory result.

A. R., a 64-yr.-old white man, had had chronic osteomyelitis of the right femur for 47 yr. During the two months prior to this hospitalization the lesion had been closed. He then had a fulminating recrudescence and was admitted to the hospital in critical condition. He was given penicillin and streptomycin. The distal femur was saucerized from the lateral side, including most of both condyles. He continued to show signs of extreme sepsis and toxicity. The infecting

organism was found to be Friedländer's bacillus. Medication was changed to bacitracin and then to terramycin. One week later a huge soft tissue abscess developed, extending from the lower third of the thigh to the lower third of the leg. Arterial and venous occlusion was manifest by gangrene of the toes. The abscess was opened above and below but not across the middle third where it passed beneath the insertion of the hamstring muscles and the popliteal vessels. A through-and-through drain was inserted. Both the original saucerization and the later abscess were then treated for 18 days with sorethytan (20) monooleate (tween® 80). The result was unsatisfactory. Daily wet dressings of "tryptar" were then placed on the saucerized lesion, and daily irrigation with "tryptar" was used on the other lesion. On the ninth day the saucerized lesion was clean enough to be skin grafted. In 12 days the drain was removed from the other lesion, and complete healing followed.

RECURRENT CARCINOMATOUS ULCER OF THE CHEST WALL

In this case the necrotic slough was débrided. Of course, no change was affected in the viable carcinomatous tissue, nor was any expected.

C. P., a 76-yr.-old white woman, had undergone radical mastectomy five years before her present admission to the hospital. Several recurrences in the axilla and the chest wall had been previously excised or treated with radiation. When she was admitted on this occasion a carcinomatous ulcer 4 cm. in diameter was present in the thoracic portion of the old scar. It involved the fourth left costal cartilage. It was covered by a thick, tenacious, purulent exudate. Dead tissue was present around the edges and in the base. Powdered "tryptar" was applied on four successive days. At the end of this time, all dead tissue and exudate were completely removed. The cartilage showed no evidence of digestion.

DIABETIC GANGRENE

Treatment of gangrenous diabetic ulcers with trypsin has given excellent results. As shown in the following case, the necessity for amputation may be avoided (Fig. 2*B, C*).

F. D., a 65-yr.-old white diabetic woman with arteriosclerosis obliterans, had an arteriosclerotic ulcer due to local gangrene on the outer side of the left foot. When first seen, the area was 2½ in. (6.35 cm.) in diameter and covered with a black slough of dead skin which was firmly attached to the deeper structures. There were draining sinuses through which pus exuded. Cultures from the lesion showed staphylococci and diphtheroids. Continuous warm saline compresses had been used for five days without improvement. Powdered "tryptar" was first applied, without benefit. A catheter was then anchored in the dressing, and an instillation of "tryptar," 10 cc. every four hours (0.5% solution in Sorensen's buffer diluent), was given. Within 48 hr. the slough had loosened completely from its base and was removed by cutting the attachments to viable skin at the side of the ulcer. At two places in the base necrotic tendon was visible. This was not affected by the trypsin and was surgically débrided together with the fifth metatarsal area. Healing is progressing in the wound even in the face of moderately severe arteriosclerosis obliterans, and the patient is not going to require amputation.

SLOUGHING WOUND AFTER FAILURE OF SKIN GRAFT

The following case well illustrates the rapidity of tryptic débridement. It is also of interest to note that streptokinase and streptodornase had previously been used, without success.

F. B., a 51-yr.-old Negro woman, was treated a year previously for a sarcoma of the right thigh with resection and roentgen therapy. When she was first seen, a skin graft had been attempted on an unhealed area measuring 6 by 3 in. (15 by 7.6 cm.). Before grafting the base was poor and could not be excised as it was directly over the femoral vessels. A 25% take had been obtained. The rest was a slough over the ulcer (Fig. 2*D, E*). The slough was removed and "tryptar" applied to the base. Within one hour a collection of thin clear fluid 1 cm.

deep had formed in the ulcer (Fig. 2*F*). This was removed. A second application was made. Within two hours the ulcer was clean, with a fresh pink base. The crust and slough at the edge had separated and come away (Fig. 2*G*). Streptokinase and streptodornase had been tried on this lesion locally, without results. The rapid action of trypsin was impressive, and we feel that it was of definite benefit in cleaning up this ulcer.

VARICOSE ULCERS

The effect of trypsin in varicose ulcers has been most satisfactory, as shown in the following case. Removal of encrusted debris allows healing to take place.

G. S., a 66-yr.-old white woman, had severe varicose veins and a varicose leg ulcer just above the left internal malleous which had been present for two years. Saphenous ligation and stripping were performed, with great improvement, but the ulcer had a heavy gray fibrous base and was slow in healing. "Tryptar" powder, 100 mg., was applied locally. There was an immediate response. Within 30 min. a large collection of thin fluid covered the ulcer. When this was removed the base was fresh, red and vascular. This treatment was repeated daily. Epithelization progressed rapidly in the next two weeks, and complete healing was obtained.

T. J., a 64-yr.-old white woman, had chronic venous stasis of the left leg due to an old thrombophlebitis and a leg ulcer just above the left internal malleous, 6 by 3 cm. in diameter with an irregular border. Powdered "tryptar" applied to the ulceration changed the character of the base of the ulcer. A thick gray fibrin coat was removed by "tryptar" application, and the ulcer base became pink and clean. "Tryptar" was only one factor in the healing of this lesion, supplementing bed rest, elevation and daily whirlpool baths. It did successfully remove the fibrinopurulent base of the ulcer.

DECUBITUS ULCER

G. C., a 57-yr.-old Negro with carcinoma of the bladder, had a severe dirty sloughing bed sore, 20 cm. in diameter, which resisted the usual methods of cleaning, mechanical débridement and dressing. Powdered "tryptar," 500 mg., was applied twice daily. Within 48 hr. the slough could be easily removed and the base and borders were clean and pink. The sacrum was widely exposed. "Tryptar" exerted no effect on dead exposed bone and did not change the course of a hopeless condition. It did exert a local beneficial effect on the soft tissue part of the decubitus ulcer (Fig. 2*H, I*).

COMMENT

From our initial investigation of tryptic débridement, we have reached certain definite conclusions. It is evident that trypsin will definitely digest or liquefy purulent exudates and blood clot. It will also digest with varying degrees of rapidity and completeness many of the other types of necrotic body tissue. Whenever a lesion is characterized by necrosis and protein debris, trypsin will be effective in cleansing the lesion. When this indication was strictly adhered to, the results were uniformly successful. To expect it to act as an agent to combat infection is not indicated from our present knowledge of its use, since trypsin is not in itself bactericidal. The decrease or disappearance of bacteria from a lesion, which has been frequently encountered, is apparently a secondary result due to a change produced by trypsin in the mediums in which the bacteria are growing.

We have not as yet used trypsin in a sufficient number of burn cases to suggest its use in burn therapy. However, from our in vitro studies we do not feel that trypsin will show the digestion of charred skin which we had hoped it would. Complete cellular death seems to be the prerequisite for most effective tryptic activity. In fact, it seems certain that trypsin will only attack dead tissue and will not attack a living cell. This phenomenon is due, in part, to intracellular antitryptic substances.

Trypsin may be used in combination with antibacterial and antibiotic drugs. Since it is a locally acting therapeutic agent, the systemic use of antibiotics should, of course, be carried out. Both penicillin and streptomycin may be mixed with solutions of trypsin and used locally.

We have concluded that trypsin is, and should be considered, an effective adjunct to the present therapy of suppurative and necrotic lesions of many types. It may well become the local treatment of choice in infected wounds. Its use in war wounds would seem to be of great value. In the effectiveness with which it cleans a suppurating wound achieves the goal of the Dakin therapy of many years ago without any undesirable side effect. It is rapid in action, nonantigenic and nonirritating. It will not harm viable tissue and will greatly facilitate the process of tissue repair. Since it needs no special case work-up or laboratory control it could be used in forward medical installations with safety and success.

SUMMARY AND CONCLUSIONS

The successful use of tryptic débridement in fibrinopurulent empyema has suggested the possible use of trypsin in the local therapy of many other suppurative and necrotic lesions. In vitro trypsin has been found to digest gangrenous skin, normal skin, fat, fascia, blood vessels and muscle.

Trypsin may be applied either as a powder or as a wet dressing, depending on the physical characteristics and pH of the lesion. When applied in closed cavities, a histamine-like reaction occurs during the first two or three treatments. Protection against this may be achieved with an antihistaminic drug such as diphenhydramine hydrochloride (benadryl®). The surface application of trypsin has no undesirable side effects. Tryptic action is rapid. Tryptic débridement denies bacteria purulent secretions as a culture medium. It promotes tissue repair. Case reports demonstrating its use in a variety of lesions have been given.

GROWTH OF VASCULAR GRAFTS IN GROWING EXPERIMENTAL ANIMALS

A Preliminary Report

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AND
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IN RECENT years there has been an increasing use of venous and arterial grafts in the operative correction of various congenital vascular anomalies in infants and children.[1] There is, however, little or no evidence to indicate whether or not these vascular grafts grow as the patient increases in size. In an attempt to answer this question, various types of vascular grafts have been utilized to bridge experimentally produced aortic defects in growing animals.

METHOD OF STUDY

Young weanling pigs were selected as experimental animals because of their known capacity for marked increase in size over a short time. With the animals under ether anesthesia the abdominal aorta was exposed retroperitoneally through a lumbar incision. An aortic segment approximately 15 mm. in length was removed between clamps and the defect bridged by an autogenous arterial graft, an autogenous venous graft or a preserved homologous arterial graft. The Carrel technique of a continuous over-and-over suture was utilized in all animals. Size 00000 Deknatel silk suture was utilized in all cases, with one exception, in which 000000 chromic surgical gut [2] was used (No. 3). At the completion of each of the operative procedures, good pulsations were noted in the aorta proximal to the graft, in the graft, and in the aorta distal to the graft. Likewise, measurements of the external diameter of the distal and proximal aorta and the graft were essentially the same at the end of the operative procedures. After the operations the animals were permitted to grow and were killed approximately seven months later. At this time the animals weighed eight to nine times more than at the time of operation. The abdominal aortas were removed, and measurements and photographs of the grafted areas were made under conditions simulating normal aortic pressure. The grafted areas were then

This work was supported by a grant from the Chicago Heart Association.

From the Department of Surgery, University of Illinois College of Medicine.

Read at the Eighth Annual Meeting of the Central Surgical Association, Chicago, Feb. 24, 1951.

1. (*a*) Gross, R. E.; Hurwitt, E. S.; Bill, A. H., and Peirce, E. C.: Preliminary Observations on the Use of Human Arterial Grafts in the Treatment of Certain Cardiovascular Disorders, New England J. Med. **239**:578, 1948. (*b*) Gross, R. E.; Bill, A. H., and Peirce, E. C.: Methods for Preservation and Transplantation of Arterial Grafts, Surg., Gynec. & Obst. **88**:689, 1949. (*c*) Johnson, J.; Kirby, C. K.; Griefenstein, F. E., and Castilla, A.: The Experimental and Clinical Use of Vein Grafts to Replace Defects of Large Arteries, Surgery **26**:945, 1949.

2. Supplied by Ethicon Suture Laboratories, New Brunswick, N. J.

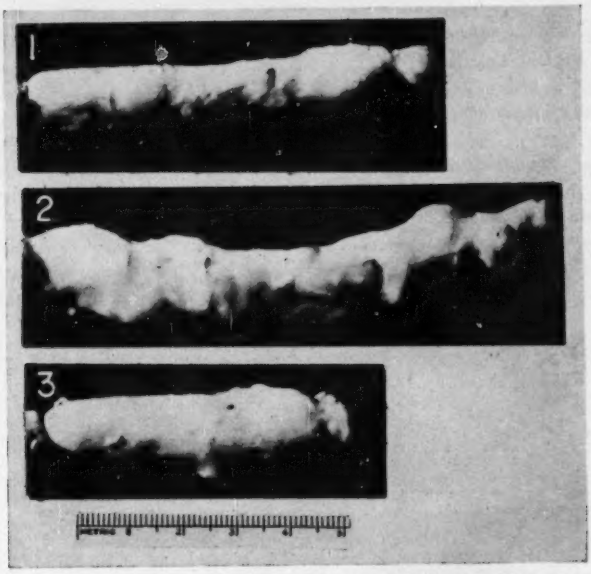

Fig. 1.—Autogenous arterial graft under conditions simulating normal aortic pressure.

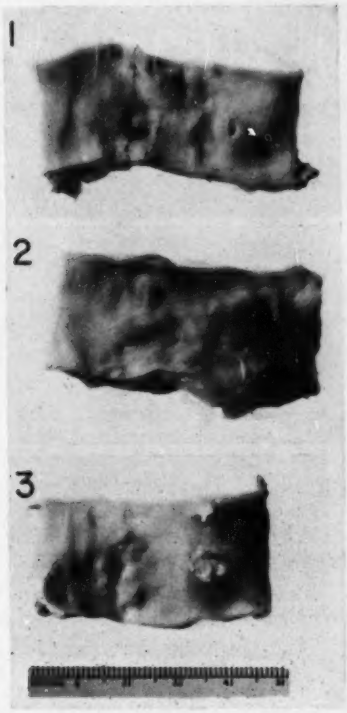

Fig. 2.—Autogenous arterial grafts opened longitudinally. Note absence of any constrictions.

opened lengthwise, photographed, and measured. Sections of the grafts and adjacent aorta were taken for histologic study.[2a]

RESULTS

Autogenous Arterial Grafts.—In three animals a segment of the aorta was removed, turned around and sutured back in place. All these grafts (Fig. 1) were patent and by measurement were found to have approximately doubled in length since implantation. The external diameters of the grafts were similar to the external diameters of the adjacent aorta. When these specimens were opened longitudinally (Fig. 2), no internal constriction of the grafts was present. (Note

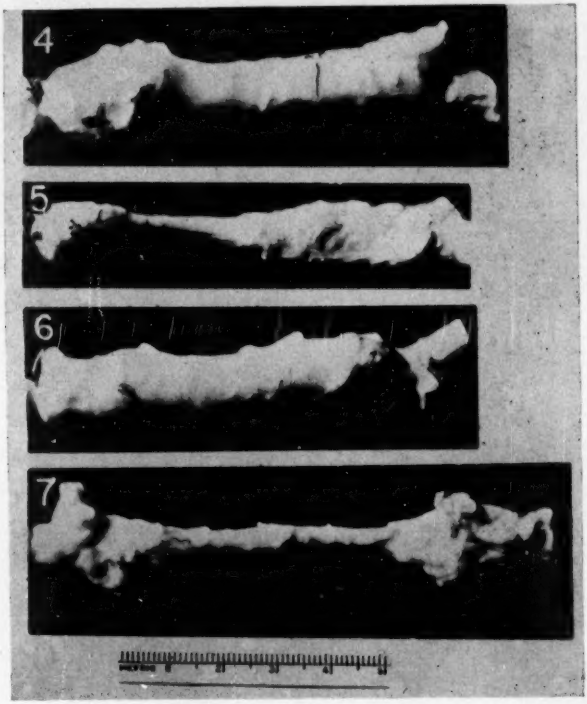

Fig. 3.—Autogenous venous grafts under conditions simulating normal aortic pressure.

the ring of endothelialization over the suture in No. 2.) Histologically the grafts remained viable for the most part. The greatest distortion and alteration occurred in the region of the sutures and involved the aortic edge as well as that of the graft. In this region there were considerable fibrosis and scarring, with destruction and loss to a greater or less extent of the elastic lamellas of both aorta and graft.

Autogenous Venous Grafts.—In four animals autogenous venous grafts (inferior vena cava) were used to bridge the experimentally created aortic defects. Two of

2a. Dr. Cecil Krakower, Professor of Pathology, examined and described the histologic sections.

these grafts (No. 4 and No. 6) (Fig. 3) were patent and had approximately doubled in length since the original operation. Their external diameters were again essentially the same as the external diameters of the adjacent aorta. In two of the four autogenous venous grafts (No. 5 and No. 7) the grafts became lengthened,

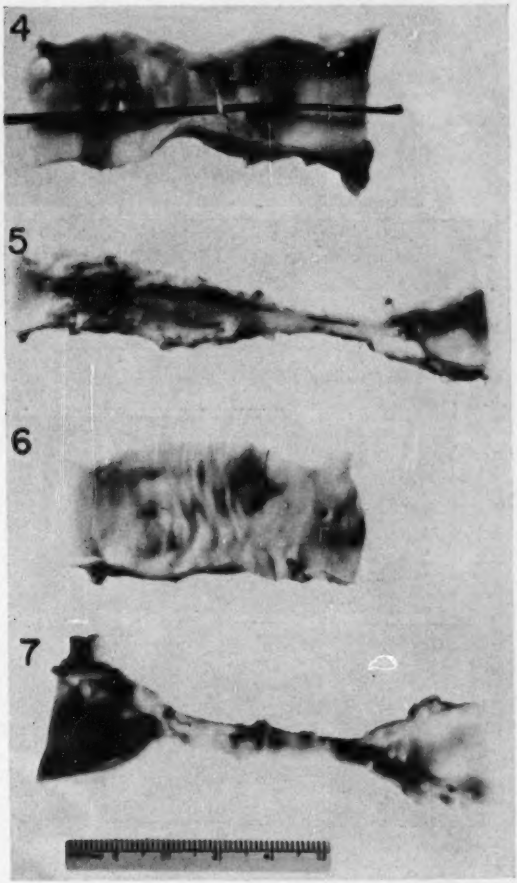

Fig. 4.—Autogenous venous grafts opened longitudinally. Note occlusion of grafts No. 5 and No. 7.

narrowed, and occluded. When the specimens were opened longitudinally (Fig. 4), no marked internal constriction of the patent grafts was observed. There was, however, notable thickening of the wall in these grafts. There was endothelialization of the suture which projected into the lumen of the vessel in one animal (No. 4). On histologic study of the two occluded grafts, it was noted that in one instance

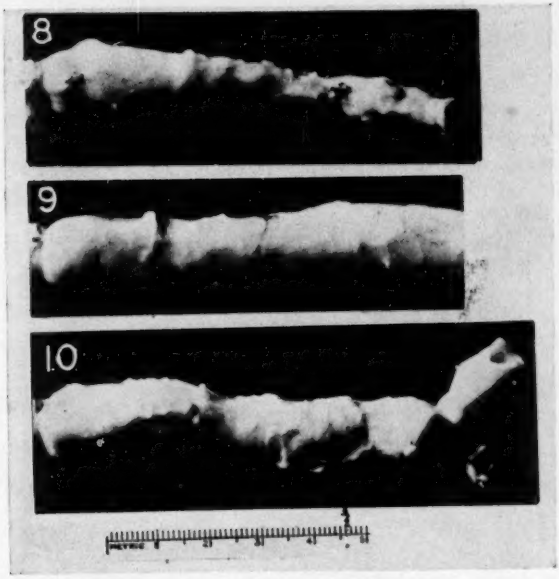

Fig. 5.—Preserved homologous arterial grafts under conditions simulating normal aortic pressure.

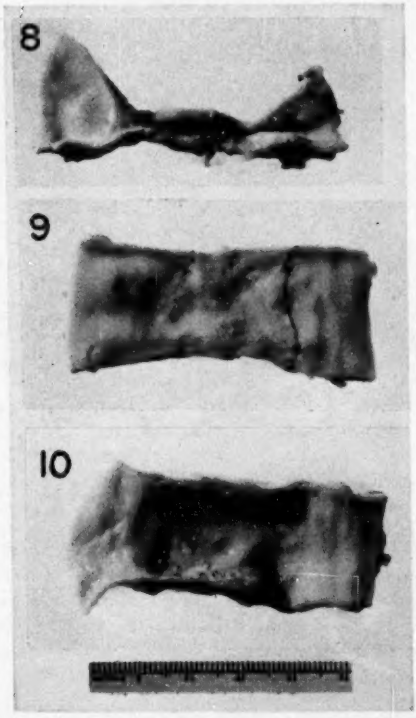

Fig. 6.—Preserved homologous arterial grafts opened longitudinally. Note occlusion of graft No. 8 and thickening of wall in graft 10.

there was a sharp reactive inflammatory change occurring about the sutures. However, in the second occluded graft, the sutures were well secured by dense fibrous tissue. The reason for lengthening of the occluded grafts is not clear, although it may well represent the stretch placed on the graft during the growth of the animal. Histologic study of the patent venous grafts revealed findings similar to those already described in the surgical literature.

Homologous Preserved Arterial Grafts.—In three animals a preserved homologous arterial (aortic) graft was inserted (Fig. 5). The grafts were preserved according to the method described by Gross,[18a] i. e., at 4 C in a modified Tyrode solution. The graft in one animal (No. 8) was not patent (specimen preserved 10 days). The grafts in two animals (No. 9, graft preserved three days; No. 10, graft preserved 10 days) were patent and had increased appreciably in length since operation. Again the external diameters of the two patent grafts were similar to the external diameters of the adjacent aorta. When the specimens were opened

Growth of Vascular Grafts (Measured in Millimeters)

	Length		External Diameter	
	Initial	Final	Initial	Final
Autogenous Arterial (Aortic Grafts)				
Pig 1	11	21	7	11
Pig 2	15	29	7	12
Pig 3	13	22	6	15
Autogenous Venous (Vena Cava) Grafts				
Pig 4	14	27	7	13
Pig 5	14	62	6	3 (graft occluded)
Pig 6	16	35	7	13
Pig 7	14	58	7	4 (graft occluded)
Homologous Preserved Arterial (Aortic) Grafts				
Pig 8	14	24	7	5 (graft occluded)
Pig 9	15	33	7	12
Pig 10	22	31	7	14

longitudinally (Fig. 6), it was noted that there were thickening and irregularity of the wall of the graft in specimen No. 10. Histologically the preserved arterial grafts did poorly, although the diameter of the lumen was maintained in two of the grafts. It is clear that the viability of these grafts was minimal. It is probable that the stenosis in specimen No. 8 was due to early necrosis of the graft and to possible early mural thrombosis with resultant intense inflammatory reaction in the original media leading to scarring of the original graft. In the other two preserved grafts, despite necrosis and calcification the elastic lamellas served in part as a framework through which smooth muscle cells and fibrocytes could grow.

The growth in length and external diameter of the various grafts is recorded in the table. Those grafts which remained patent, whether autogenous arterial, autogenous venous, or homologous preserved arterial grafts, grew in both length and diameter. The patent grafts in general were twice as long as when they were inserted. Likewise, the external diameters of the grafts grew to such an extent that there was no significant disparity between the external diameter of the grafted area and the external diameters of the adjacent aorta.

SUMMARY

Autogenous arterial, autogenous venous and homologous preserved arterial grafts were inserted into aortic defects in 10 young pigs to determine if the grafts would grow as the animals increased in size. Three of three autogenous arterial grafts, two of four autogenous venous grafts, and two of three homologous preserved arterial grafts were patent when the animals were killed seven months later after a weight increase of eight to nine times. All grafts which remained patent grew appreciably in both length and diameter. More extensive studies are now in progress to determine if there is a statistically significant difference in incidence of occlusion between autogenous venous and homologous preserved arterial grafts in growing experimental animals.

Case Reports, New Instruments and Techniques

NEW NEEDLE FOR USE WITH WIRE SUTURE MATERIAL

GEORGE P. ROSEMOND, M.D.
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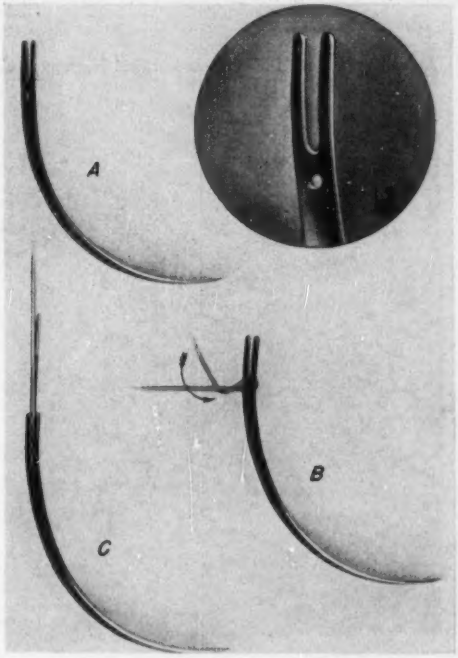
ALLOY steel wire as a suture material was introduced to the medical profession by Dr. W. Wayne Babcock in 1934.[1] It has attained wide popularity among surgeons because it is completely nonirritating, and its tensile strength is great.



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From the Temple University School of Medicine and Hospital.

1. Babcock, W. W.: Ligatures and Sutures of Alloy Steel Wire, J. A. M. A. **102**:1756 (May 26) 1934.

tage. The use of atraumatic needles with the wire fixed into the needle is satisfactory but expensive. Braided wire has been tried and has proved much more flexible and usable than ordinary wire, and the twisted base tends to be smaller, but again the ends tend to fray and the expense is increased.

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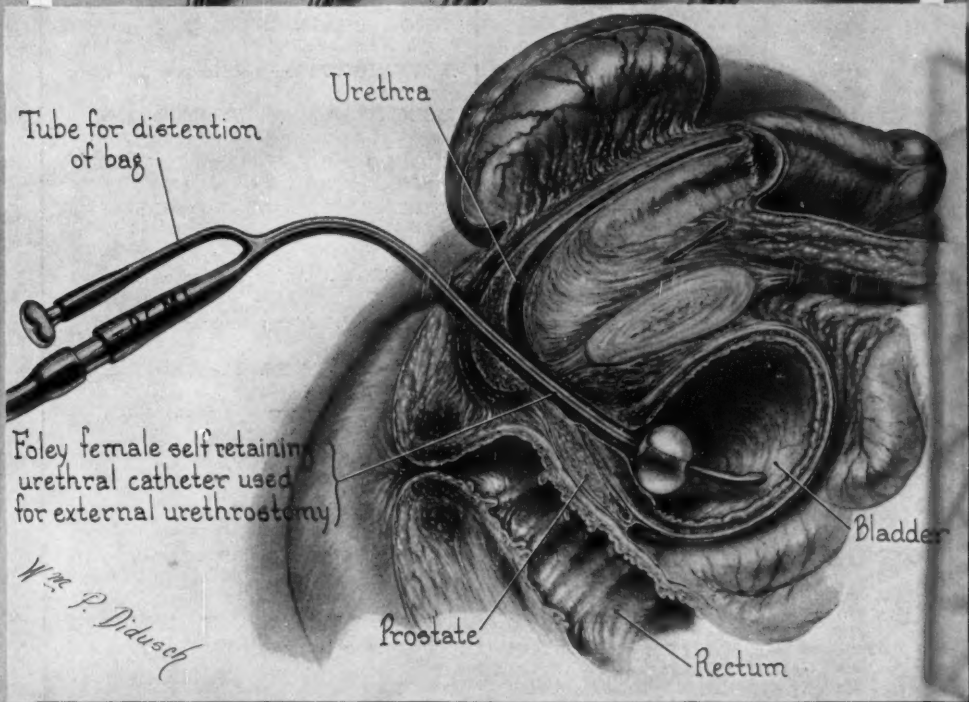

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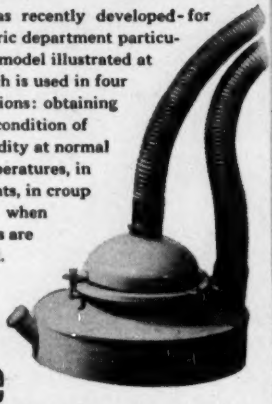

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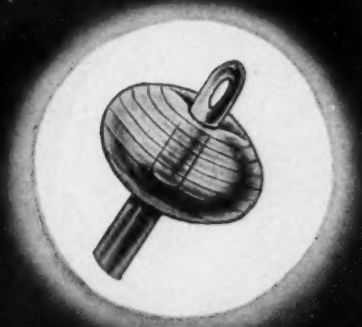

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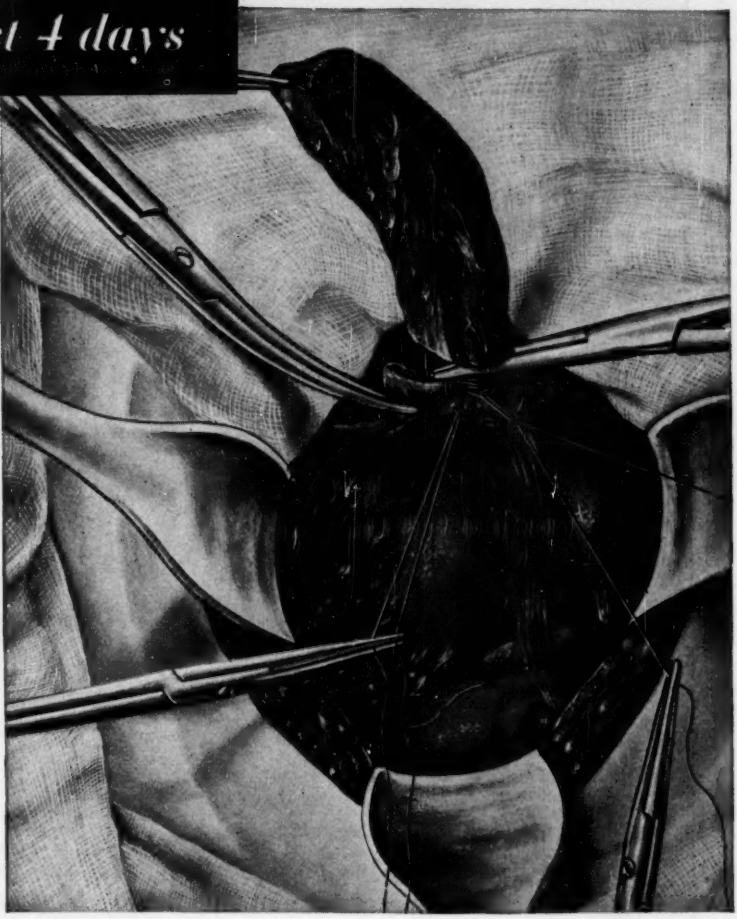

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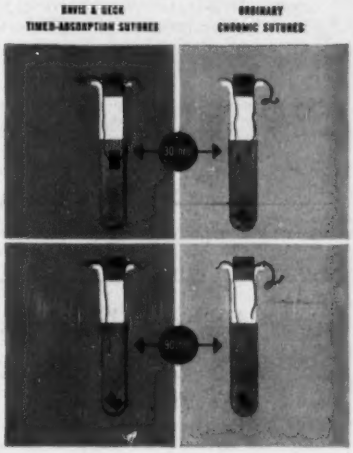

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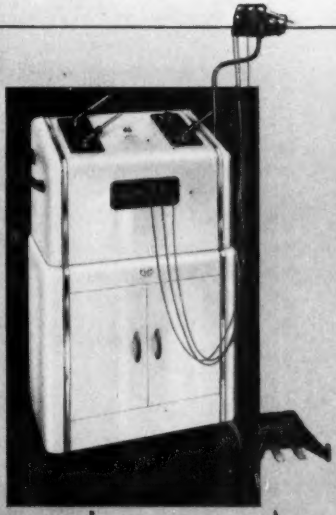

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